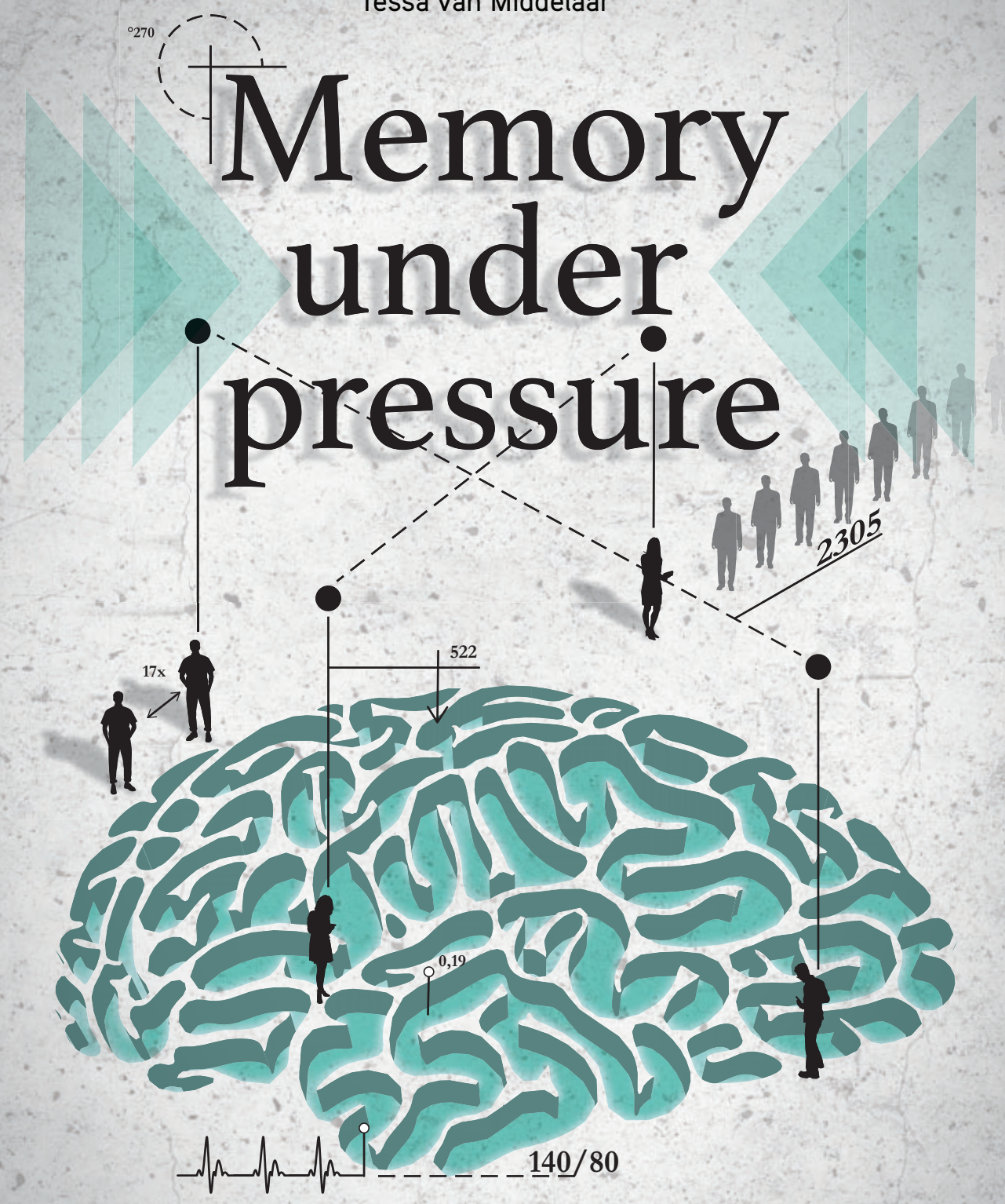
Tessa van Middelaar

Memory under pressure



DONDERS SERIES

Blood pressure management to prevent dementia

MEMORY UNDER PRESSURE:

BLOOD PRESSURE MANAGEMENT TO PREVENT DEMENTIA

Tessa van Middelaar

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MEMORY UNDER PRESSURE:

BLOOD PRESSURE MANAGEMENT TO PREVENT DEMENTIA

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GENERAL INTRODUCTION

1

DEMENTIA

The number of people with dementia worldwide is projected to triple in the coming thirty years, from 47 to 135 million.[1] This amplification is mainly driven by population ageing; an increase in the number and proportion of older people.[2] Dementia is a clinical diagnosis characterised by cognitive impairment that interferes with daily functioning.[3] It has major impact on society at the micro- and macro-level. People with dementia have severely impaired quality of life, and face increasing disability and reduced life expectancy.[4,5] The functional dependence associated with dementia leads to an increased burden on (in) formal caregiving.[6] The community as a whole is affected by costs of health- and social care, and loss in productivity, mainly due to informal care.[5] The combined annual costs are estimated at almost 700 billion euros worldwide.[5] Therefore, the G8 countries have agreed to take global action to reduce the dementia prevalence and burden, and have identified dementia prevention as a major public health priority.[7]

The two main subtypes of dementia are Alzheimer's disease and vascular dementia.[8] The first is neuropathologically characterized by beta-amyloid depositions ("plaques") and hyperphosporylated tau ("tangles"), and the second by cerebrovascular lesions. It was long presumed that the two diseases occurred exclusive of one another. However, in the last decades it became apparent that the majority of persons with dementia have both neurodegenerative and cerebrovascular pathology.[9] They also share common risk factors.[10]

The most influential risk factor for dementia is age, with around 80% of persons with dementia being 75 years or older.[11] Yet, more noteworthy are the potentially modifiable risk factors; midlife hypertension, diabetes, midlife obesity, physical inactivity, depression, smoking, hyperlipidaemia and low educational attainment.[10,12] Up to a third of dementia cases may be attributable to these modifiable risk factors.[10]

DEMENTIA PREVENTION TRIALS

The window of opportunity for interventions aimed at preventing dementia is large. It has been estimated, that if modifiable risk factors could be reduced by 10%, this could lead to a reduction in the prevalence of Alzheimer's disease of 8% within forty years.[10] This would sum up to 8.8 million people in whom dementia could be prevented. Initially, randomised controlled trials (RCTs) only included cognitive impairment and dementia as secondary outcome measures.[13] In the last three years, the first trials with cognition or dementia as primary outcome have been published. The *Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability* (FINGER) and *Multidomain Alzheimer Preventive Trial* (MAPT) showed that a multi-domain intervention targeting several dementia risk factors could potentially have a beneficial effect on cognition within 2-3 years in an at risk population.[14,15] The *Prevention of Dementia by Intensive Vascular Care* (preDIVA; box 1) trial,

however, did not show a beneficial effect on prevention of dementia within 6-8 years, in a general population aged 70-78 years.[16] Researchers from these three trials united their efforts in the design and execution of the *Healthy Ageing Through Internet Counselling in the Elderly* (HATICE; box 1).[17] This thesis is based on post hoc analyses in the preDIVA trial and two sub-studies in the HATICE trial.

Box 1 - Description of the preDIVA and HATICE trial

Prevention of Dementia by Intensive Vascular Care (preDIVA) is a Dutch cluster-randomised controlled trial (RCT), which ran from 2006-2016.[16] The trial studied the effect of nurse-led vascular care during 6-8 years on incident all-cause dementia. Participants randomised to the intervention group had four-monthly visits to a practice nurse during which lifestyle and medical advice was given regarding blood pressure, cholesterol, weight, smoking, physical activity and diet. Participants in the control group received standard care. For the trial community-dwelling people aged 70-78 years, without dementia, were recruited at baseline. Every two years all participants visited a trial nurse, during which primary and secondary outcome measures were assessed, including cardiovascular risk parameters and cognition. After 6-8 years an independent outcome adjudication committee validated all possible dementia cases based on clinically available data.

Healthy Ageing Through Internet Counselling in the Elderly (HATICE), is an international RCT which ran from 2015-2018 on the effect of an internet intervention for cardiovascular self-management to reduce the risk of cardiovascular disease and dementia.[17] For HATICE, people aged 65 years and older at increased cardiovascular risk were recruited to participate in the Netherlands, Finland and France. Intervention participants gained access to an interactive internet platform with remote support by a coach and several other functionalities to facilitate self-management, such as the ability to enter measurements and set goals.[18] The control group gained access to a platform with static information. After 18 months the effect of the intervention on a composite score containing systolic BP, low-density lipoprotein cholesterol and body-mass index, was assessed.

BLOOD PRESSURE AND COGNITION

Though the main result of the preDIVA trial was neutral, a significant effect of the intervention was seen among participants with untreated hypertension at baseline who were adherent to the intervention.[16] This suggests that older people with hypertension could be a good target population for preventive interventions and that BP-lowering interventions might be paramount. Because of the high prevalence of hypertension and its effective and widely implemented treatment, it is also a feasible target. In this thesis, I therefore focus on prevention of dementia through blood pressure (BP) management.

There is a clear association between a high BP in midlife and an increased risk of dementia in late life.[10] A high BP may cause microvascular dysfunction and damage leading to cerebrovascular lesions and, in turn, cognitive decline.[19] With BP in late life this relation is

less straightforward. The association between mean BP in late life and dementia may follow a J-shaped curve, meaning that both a high and low BP are associated with an increased risk (Figure 1).[20] Trials that assessed the effect of BP-lowering interventions on incident dementia are suggestive of a beneficial effect, but have not been conclusive yet.[21] Furthermore, results from observational studies have suggested that, beside a BP lowering effect, specific antihypertensive medication (AHM) classes might also have a class-specific beneficial effect on dementia.[22] The adverse relation with a low BP in people in late life, might be because an already ongoing process of neurodegeneration causes autonomic dysregulation or because problems with cerebral blood flow regulation cause cerebral hypoperfusion.[23]

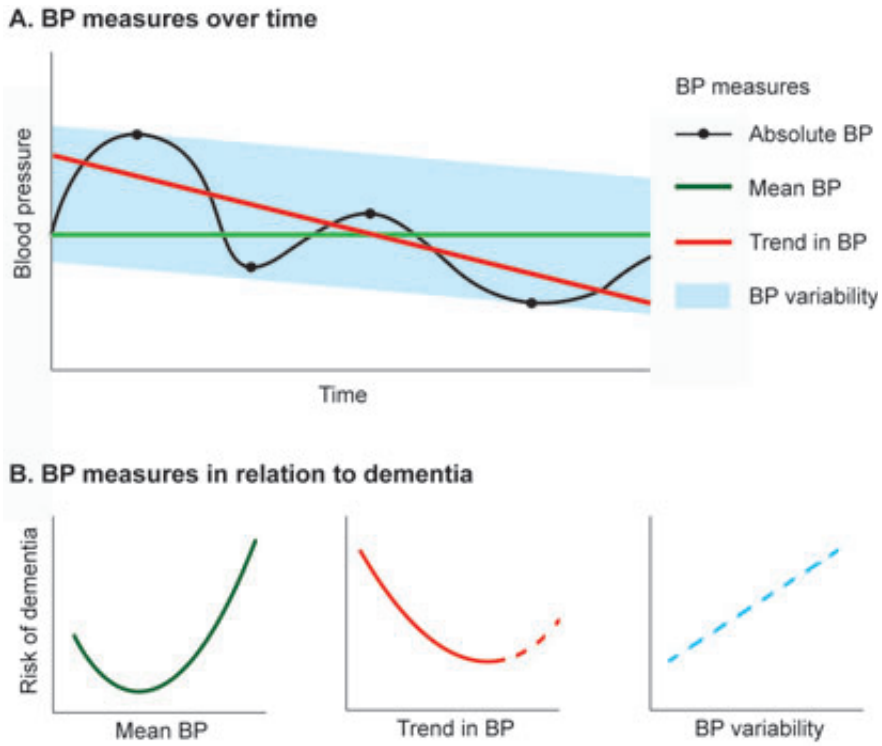

Figure 1 - Conceptual illustration of the relation between different blood pressure (BP) measures over time (A) and the (possible) association between these BP measures in late life and dementia (B). The solid line in figure 1B. represents a relation that is confirmed in observational studies and the dotted line a hypothesized relation. The relation between mean BP (green line) and risk of dementia follows a J-shaped curve, indicating that both higher and lower BP levels are associated with an increased risk of dementia.[20] A declining trend (trend line) in BP is associated with an increased risk of dementia.[25] Such an association has not been established for increasing trend in BP in late life, but it is likely that also steep increases are unfavourable. A higher BP variability is hypothesized to be associated with an increased risk of dementia.[26]

There is limited available evidence on the effect of AHM deprescription (that is, decrease or discontinue AHM).[23] One relatively small trial showed that discontinuation of AHM was safe, but did not have a beneficial effect on cognition within 16 weeks.[24] In addition, there is evidence suggesting that not only mean BP is of prognostic value, but also changes over time, such as a declining BP or BP variability (Figure 1).[25,26] BP variability is associated with cardiovascular disease and mortality and may also cause cognitive deficits due to cerebral small vessel disease (SVD).[27] It is important to clarify the relation between BP in late life and dementia, as most prevention trials target older populations, and lower may not always be better.

METHODOLOGICAL CHALLENGES

Dementia prevention trials face methodological challenges in at least four stages of the study design: selection and recruitment of the target population, adherence to the intervention and selection of a suitable outcome measure. The lack of a beneficial effect of the preDIVA intervention may be (partially) attributable to the unselected, population-based recruitment strategy, including participants with a relatively low or average baseline risk. It is conceivable that targeting a high-risk population would yield a larger window of opportunity for dementia prevention. Also, the optimal age range for the target population is unclear; dementia incidence is higher at older ages, but with increasing age the effect of the intervention might also diminish.[28] External validity of trial results is, among other factors, dependent on recruitment methods. Understanding people's reasons for deciding to participate or not has the potential to improve recruitment and external validity of study findings. After recruitment of the study population, the next challenge, for non-pharmacological prevention trials in particular, is adherence to the intervention. It is difficult to instigate a lifestyle improvement, but it is even more strenuous to make a lifestyle change sustainable.[29] Finally, very few trials have the opportunity to select dementia as primary outcome, as it requires a long intervention duration and a large study population to demonstrate an effect. Ongoing and future trials will, therefore, often have intermediate outcome measures. A good intermediate outcome measure needs to be sensitive to an intervention effect and it should be reliable to generalise an effect on the intermediate outcome measure to an effect on incident dementia. Intermediate outcome measures that are currently used are cognition and measures of cardiovascular risk. Another proposed intermediate outcome measure is cerebral SVD, a radiological marker of damage to the small cerebral vasculature.[30]

AIM AND OUTLINE OF THE THESIS

This thesis is focused on the prevention of dementia through BP management.

In **part I** of this thesis we aim to unravel the complex relation between BP in late life and incident dementia. First of all, by updating the literature on the preventive effect of BP-lowering interventions on incident dementia, with a systematic review and meta-analysis (**chapter two**). In **chapter three** we assess whether there is a class-specific effect of AHM in the prevention of dementia within the preDIVA study population. Within this study population we also assess whether BP variability is associated with incident dementia (**chapter four**). In **chapter five** we present the results of semi-structured interviews with Dutch general practitioners to describe how they deal with the ambiguity in evidence regarding AHM (de)prescription in older people, in daily clinical practice.

In **part II** of this thesis we tackle some of the previously mentioned methodological challenges in dementia prevention trials. In **chapter six** we investigate whether the preDIVA intervention was more effective among participants with a high modifiable dementia risk score, to assess whether such a risk score might be useful to select trial participants. In two sub-studies among HATICE participants we studied reasons for participating in HATICE (**chapter seven**) and factors that influence initial and sustained engagement with the intervention (**chapter eight**). In **chapter nine** we assess whether it is possible to intervene in the progression of cerebral SVD, with a systematic review and meta-analysis on the preventive effect of AHM, to see if it might be eligible as intermediate outcome measure for future trials.

In **chapter ten** we provide a general discussion of the presented results. We discuss how the different studies are interlinked, what they add to current literature and what their implications are on clinical practice and future research. **Chapter eleven** of this thesis provides an overall summary.

BLOOD-PRESSURE-LOWERING INTERVENTIONS TO PREVENT DEMENTIA

A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Our objective was to study the preventive effect of lowering blood pressure (BP) by medication and/or lifestyle changes on incident all-cause dementia, Alzheimer's disease and vascular dementia. In this systematic review we included randomized controlled trials with a BP-lowering intervention. Of the nine included trials seven assessed the effect of antihypertensive medication and two of a lifestyle or combined intervention. In the intervention arm, 1041 out of 29029 (3.6%) participants were diagnosed with dementia compared to 1090 out of 28653 (3.8%) controls during a median follow-up of 3.9 years [range 2-10], resulting in a pooled risk ratio (RR) of 0.93 (95% confidence interval [CI] 0.84-1.02; I^2 16%). Three trials specified dementia subtypes, with no significant effect on Alzheimer's disease or vascular dementia. To conclude, lowering BP by medication and/or lifestyle changes did not lead to a significantly reduced risk of dementia. This appeared independent of dementia subtype.

INTRODUCTION

The number of people diagnosed with dementia worldwide is anticipated to triple between 2015 and 2050, due to an increasingly ageing population.[2] Up to a third of Alzheimer's disease cases are attributable to potentially modifiable risk factors, with (midlife) hypertension accounting for 5%.[10] The high prevalence of hypertension and the widely implemented and relatively inexpensive blood pressure (BP)-lowering interventions render it suitable as prevention target.[31,32]

In spite of the potential of BP-lowering interventions to prevent dementia, such a preventive effect has not been convincingly documented.[21,33] In two meta-analyses, published in 2008[21] and 2009[33], there was a suggestion of a preventive effect of lowering BP on incident dementia with, respectively, a hazard ratio of 0.87 (95% confidence interval [CI] 0.76-1.00) and an odds ratio of 0.89 (95% CI 0.74-1.07). These previous meta-analyses confined their scope to the effect of antihypertensive medication or to participants without a history of cerebrovascular disease. Lifestyle changes are an important aspect of BP-lowering interventions in current clinical guidelines and can lead to substantial BP reductions.[31,34] In addition, two large trials with lifestyle interventions have recently been published.[16,35]

Our primary aim was to study the preventive effect of lowering BP by medication and/or lifestyle changes, on incident all-cause dementia. Our secondary aim was to study the preventive effect on the dementia subtypes Alzheimer's disease and vascular dementia.

METHODS

This systematic review was performed following the *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) statement and the protocol was registered in Prospero (CRD42017056875).[36,37]

Data Sources and Searches

We searched MEDLINE, EMBASE, PsycInfo, the Cochrane Library, the *Cumulative Index to Nursing and Allied Health Literature* (CINAHL), Web of Science, clinicaltrials.gov and World Health Organization international clinical trials register platform up to August 29th 2017. The search included related terms for randomized controlled trial (RCT), dementia and BP-lowering interventions, including specific antihypertensive drugs and lifestyle changes (Supplementary Appendix S1: full search strategy). The reference lists of the included articles and systematic reviews of interest were additionally searched for potentially eligible studies.

Study Selection

Two authors (T.v.M. and L.A.v.V. or E.M.F.S.) independently assessed all articles, first based on their titles and abstracts and then based on their full text. Disagreement was resolved by consulting a third author (E.R.). We included studies that matched the following criteria: RCT; BP-lowering intervention with medication and/or a lifestyle changes; incident dementia according to internationally accepted criteria as primary or secondary outcome; and at least 200 participants. An intervention was considered BP-lowering if it was generally accepted in allopathic medicine and if the (reported) goal of the intervention was to reduce BP or if BP at baseline and follow-up (or change during follow-up) were reported. Studies with multi-domain interventions (that is, also including other intervention targets such as cholesterol) were also included, as long as BP was one of the targets of the intervention. No restriction was applied on the control condition or to whether BP-lowering concerned primary or secondary cardiovascular prevention (that is, we included study populations with and without a history of cardiovascular disease). We excluded studies with solely institutionalized patients (such as nursing home residents), as they consist of a multi-morbid population that is substantially different from the general or hospital-based population. Only articles published in English were included. For our secondary aim, the definition of Alzheimer's disease and vascular dementia used in the individual trials was adopted.

Data Extraction and Quality Assessment

Data from the included trials were extracted independently by two authors (T.v.M. and E.M.F.S.) following a predefined data extraction form including study characteristics, baseline characteristics, content of the intervention and control group, dementia incidence, mortality incidence and funding sources. Risk of bias was assessed with the Cochrane risk of bias assessment [38] and quality of evidence following the *Grading of Recommendations, Assessment, Development and Evaluations* (GRADE) approach.[39] Authors from the included trials were contacted in case data necessary for meta-analysis were not published.

Data Synthesis and Analysis

Data on incident dementia, Alzheimer's disease and vascular dementia were pooled into risk ratios (RR) according to the DerSimonian-Laird random effects model.[40] Statistical heterogeneity between the studies was assessed with I^2 statistic and risk of publication bias with a funnel plot.[40] We performed subgroup analyses on population characteristics by pooling trials that only included people aged at least 70 years, with a history of stroke and with type 2 diabetes, and a subgroup analysis on the nature of the intervention (pharmacological versus lifestyle intervention). With meta-regression analysis we assessed the influence of duration of the intervention, mean age at baseline, difference in systolic

BP (SBP) at follow-up between the intervention and control group, SBP at baseline and follow-up in the intervention group and decrease of SBP during follow-up. If SBP at baseline, follow-up or decrease during follow-up was not documented, it was either calculated based on the data that was available (for example, decrease calculated by subtracting SBP at baseline from SBP at follow-up) or data reported in the (primary) publication of the entire trial population was used. A class-specific protective effect is hypothesized for several antihypertensive drug classes aside from their potentially protective effect through BP-lowering.[41] To compare the effect of different classes of antihypertensive medication we used pairwise meta-analysis. For this analysis we defined class according the drug used as (primary) intervention, and did not take off-label or additional drug use into account. Originally, we intended to perform a network meta-analysis, but the number of trials with different classes of antihypertensive medication was deemed too low and trials were only placebo-controlled, rendering indirect treatment comparisons unreliable. We included a description of competing risk analyses performed in the individual trials and a pooled RR on mortality, to assess the potential influence of mortality as competing risk for dementia. As BP-lowering is effective in reducing the risk of mortality,[31] the number of participants at risk of dementia and their mean age might inadvertently be higher in the intervention group, thereby attenuating potential effects on dementia. If mortality rates were only reported from the entire trial population and not separate for the subset with information on dementia, this data was used. All data were analysed using R studio (version 3.4.3; Boston, Massachusetts, United States of America) package meta for the statistical analysis.[42]

RESULTS

We identified 5164 individual articles, of which 179 were included based on title and abstract (Figure 1). After careful reviewing of the full text, 17 articles reporting on nine individual trials were included for meta-analysis.[16,21,35,43-48] One trial was excluded because the authors could not provide separate data on dementia.[49]

Quality assessment

Table S1 in the online supplement shows the risk of bias assessment. Overall the risk of bias was low, with the exception of the *Prevention of Dementia by Intensive Vascular care* (preDIVA) and *Look Action for Health in Diabetes* (Look AHEAD) trial, that had a high risk of performance bias, as participants and personnel were not blinded due to the nature of the intervention (a lifestyle or combined intervention).[16,35] In the *Prevention Regimen for Effectively Avoiding Second Strokes* (PRoFESS) trial the sponsor was involved in the study design, collection, analysis and interpretation of the data, creating risk of bias.[48] The sponsor was however not involved in the decision to submit the paper for publication. Additional

data on dementia incidence was supplied by authors from the *Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation* (ADVANCE) trial.[47] In the funnel plot (Supplementary Figure S1) the *Systolic Hypertension in Europe* (Syst-Eur) trial was considered an outlier, with a relative high standard error and low risk ratio of 0.47.[44] Aside from this there was no pattern indicative of publication bias. The GRADE level of evidence was assessed as high.

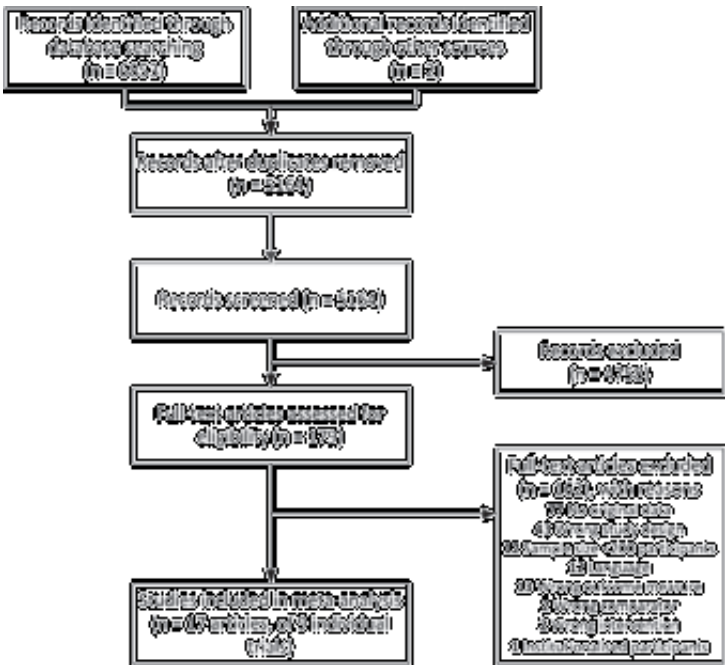

Figure 1 - Flowchart of study selection

Study characteristics

Among the different trials, three included people aged at least 70 years, two trials were conducted in patients with a history of stroke and two among people with type 2 diabetes (Table 1). In all trials mean age at baseline was at least 60 years and in four trials participants had a mean baseline SBP more than 160 mmHg (Table 2). Seven trials assessed the effect of antihypertensive medication and two of a lifestyle or combined intervention. Four trials studied the effect of a multi-domain intervention which also targeted for example cholesterol or physical activity.[16,35,47,48] Median intervention duration was 3.9 years [range 2-10]. Two studies had an observational extended follow-up of 1.5 years after the intervention period ended (to 3.9 and 11.4 years after baseline).[35,44]

Table 1 - Study characteristics

Trial	Year	Commercial (co)funder[a]	Intervention	Control	Inclusion criteria	Duration (years)
SHEP[43]	1991	No	Chlorothalidon (add-on atenolol or reserpine)	Placebo	Age ≥60 years, mean SBP 160-219 mmHg and DBP <90 mmHg	4.5
Syst-Eur[44]	2002	Yes	Nitrendipine (add-on enalapril and/or hydrocholorothiazide)	Placebo	Age ≥60 years, SBP 160–219 mmHg and DBP <95 mmHg	2 (extended FU 3.9)
SCOPE[45]	2003	Yes	Candesartan (add-on hydrochlorothiazide)	Placebo	Age 70–89 years, SBP 160–179 mmHg and/or DBP 90–99 mmHg	3.7
PROGRESS[46]	2003	Yes	Perindopril and indapamide	Placebo	History of cerebrovascular disease (stroke or TIA, no SAH) within the previous 5 years	3.9
ADVANCE[47]	2007	Yes	Perindopril and indapamide[b]	Placebo	Age ≥55 years, diabetes type 2 and increased cardiovascular risk	4.3
HYVET-COG[21]	2008	Yes	Indapamide (add-on perindopril)	Placebo	Age ≥80 years, sitting SBP 160-199 mmHg, standing SBP ≥140 mmHg, DBP <110 mmHg	2.2
PROFESS[48]	2008	Yes	Telmisartan[c]	Placebo	Age ≥55 years, ischemic stroke in previous 90 days[d]	2.4
PreDIVA[16]	2016	No	Intensive vascular care	Standard care	Age 70-78 years	6.7
Look AHEAD[35]	2017	No	Intensive lifestyle intervention	Diabetes support and education	Age 45-75 years, diabetes type 2, SBP <160 mmHg, DBP <100 mmHg[e]	9.8 (extended FU 11.4)

[a] A list of the trials funding can be found in the online supplement (table e-4). [b] 2-by-2 factorial design combined with intensive glucose control. [c] 2-by-2 factorial design combined with acetylsalicylic acid and extended-release dipyridamole or clopidogrel. [d] If a patient was aged 50-54 years or presented 90 to 120 days after the qualifying stroke they were also included if they had an increased cardiovascular risk. [e] Additional inclusion criteria: BMI ≥25, HbA1c ≤11%, triglyceride <6.77 mmol/L and safe to exercise. ADVANCE, Action in Diabetes and Vascular disease preterAx and diamicroN-MR Controlled Evaluation; FU, follow-up; HbA1c, Glycosylated Hemoglobin, Type A1C; HYVET-COG, Hypertension in the Very Elderly Trial cognitive function assessment; Look AHEAD, Look Action for Health in Diabetes; PreDIVA, Prevention of Dementia by Intensive Vascular Care; PRoFESS, Prevention Regimen for Eff ectively Avoiding Second Strokes; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; SAH, subarachnoid haemorrhage; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic Hypertension in Europe; TIA, transient ischaemic attack.

Table 2 - Participant characteristics

	N= (interv. / control)	Age (years)[a]	Sex (male)[a]	BP at baseline[a]	BP at FU interv.	BP at FU control
SHEP[43]	2365 / 2371	72 (7)	1034 (44%)	171 (10) / 77 (10)	144 (19) / 68 (10)	155 (21) / 71 (13)
Syst-Eur[44]	1485 / 1417	70 (7)	416 (34%)	174 (10) / 86 (6)	149 (10) / 79 (6)	156 (12) / 83 (6)
SCOPE[45]	2477 / 2460	76 (n.r.)	872 (35%)	166 (9) / 90 (7)	145 (16) / 80 (9)	149 (17) / 82 (9)
PROGRESS[46]	3051 / 3054	64 (10)	2136 (70%)	147 (19) / 86 (11)	±132 (n.r.) / 78 (n.r.)[b]	±142 (n.r.) / 82 (n.r.)[b]
ADVANCE[47]	5569 / 5571	66 (6)	3203 (58%)	145 (22) / 81 (11)	136 (n.r.) / 73 (n.r.)	140 (n.r.) / 73 (n.r.)
HYVET-COG[21]	1687 / 1649	84 (3)	664 (39%)	173 (9) / 91 (9)	143 (n.r.) / 76 (n.r.)	160 (n.r.) / 84 (n.r.)
PROFESS[48]	4690 / 4680	66 (9)	6527 (64%)	144 (16) / 84 (11)	±136 (n.r.) / 78 (n.r.)[b]	±138 (n.r.) / 79 (n.r.)[b]
PreDIVA[16]	1890 / 1636	75 (3)	850 (45%)	156 (22) / 81 (11)	148 (19) / 77 (11)	150 (21) / 79 (11)
Look AHEAD[35]	1918 / 1884	70 (range 55-87)	760 (40%)	128 (17) / 70 (10)	126 (95% CI 125-127) / 66 (95% CI 66-67)	127 (95% CI 127-128) / 66 (95% CI 66-66)

Mean (standard deviation) and number (percentage) are presented unless stated otherwise. [a] As characteristics at baseline were comparable in the intervention and control group due to randomisation, only results from the intervention group are presented. [b] Blood pressure was estimated based on a figure. ADVANCE, Action in Diabetes and Vascular disease preterAx and diamicroN-MR Controlled Evaluation; BP,
blood pressure; CI, confidence interval; FU, follow-up; HYVET-COG, Hypertension in the Very Elderly Trial cognitive function assessment; Interv., intervention; Look AHEAD, Look Action for Health in Diabetes; n.r., not reported; PreDIVA, Prevention of Dementia by Intensive Vascular Care; PROFESS, Prevention Regimen for Effectively Avoiding Second Strokes; PROGRESS, Perindopril Protection Against Recurrent Stroke Study; SAH, subarachnoid haemorrhage; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; Syst-Eur, Systolic Hypertension in Europe; TIA, transient ischemic attack.

Primary analyses

Dementia was the primary outcome measure in the preDIVA trial,[16] while the other trials included it as secondary outcome. In total, 1041 out of 29029 participants (3.6%) were diagnosed with incident dementia in the intervention group and 1090 out of 28653 (3.8%) in the control group, resulting in a pooled RR of 0.93 (95% CI 0.84-1.02; I^2 16%; Figure 2).

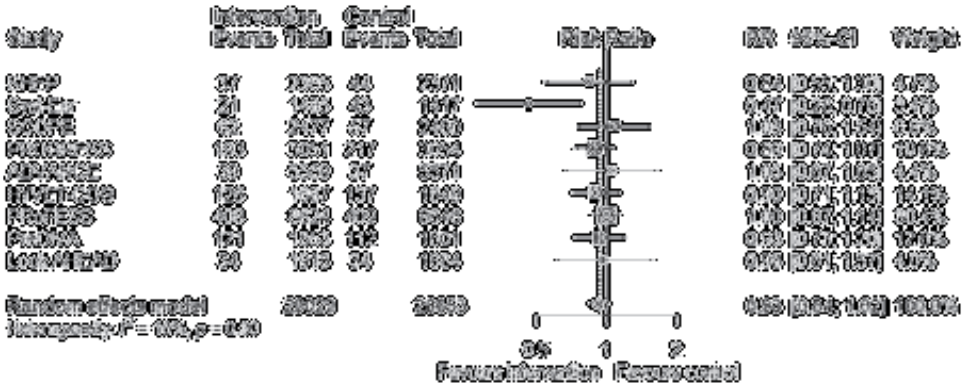

Figure 2 - Forest plot on the effect of BP-lowering interventions on incident all-cause dementia
RR indicates risk ratio; CI, confidence interval.

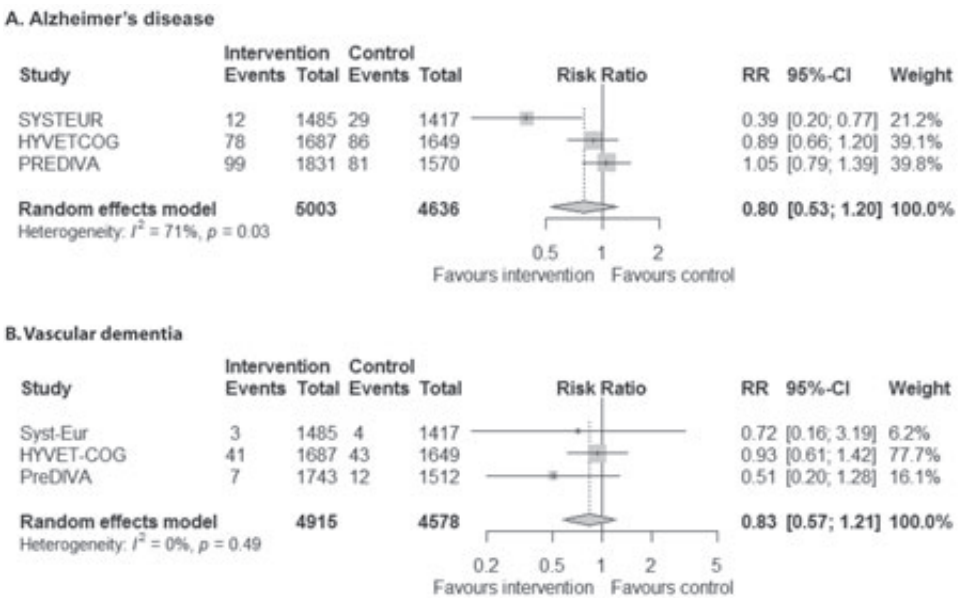

Figure 3 - Effect of blood pressure lowering treatment on Alzheimer's disease (A) and vascular dementia (B)

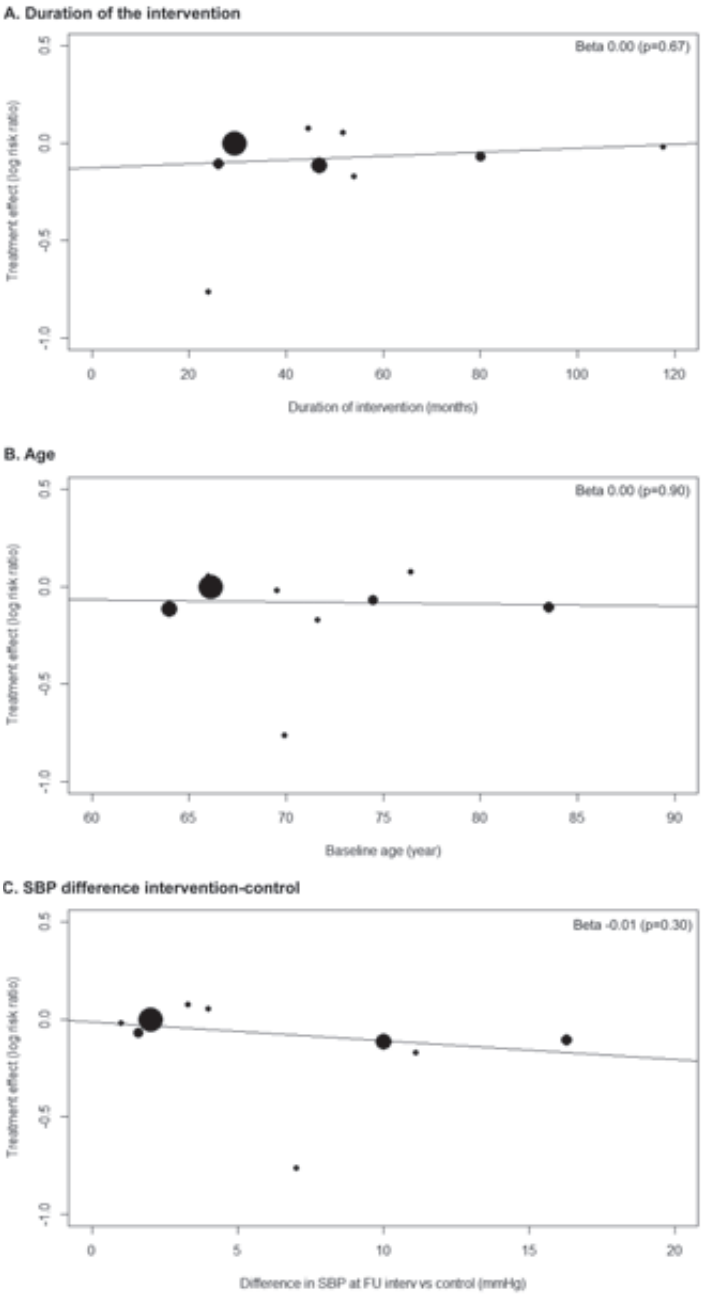

Figure 4 - Meta-regression assessing the influence of duration (A), age (B) and difference in systolic BP between treatment arms at follow-up (C) on the effect of BP-lowering interventions to prevent dementia

SBP indicates systolic blood pressure; FU, follow-up; interv., intervention.

Dementia incidence rates ranged between 1.6 cases/1000 persons/year in the two studies with (relatively young) diabetes patients and 36.4 cases/1000 persons/year in the trial with people ≥80 years (Supplementary Table S2).[21,35,47] Excluding the Syst-Eur trial as outlier from the meta-analysis resulted in a RR of 0.96 (95% CI 0.88-1.04; I^2 0%). Three trials registered the subtype of dementia.[16,21,44] BP-lowering interventions did not significantly reduce the number of incident Alzheimer's disease cases (RR 0.80; 95% CI 0.53-1.20; I^2 71%; Figure 3A) or vascular dementia cases (RR 0.83; 95% CI 0.57-1.21; I^2 0%; Figure 3B).

Subgroup and sensitivity analyses

Subgroup analyses showed no effect in populations with solely participants aged ≥70 years (RR 0.94; 95% CI 0.84-1.10; I^2 0%), with history of a stroke (RR 0.96; 95% CI 0.86-1.07; I^2 0%), or with diabetes (RR 1.02; 95% CI 0.74-1.41; I^2 9%; Supplementary Figure S2). No differences were noticeable in the subset of trials with a purely pharmacological intervention (RR 0.92; 95% CI 0.80-1.04; I^2 37%) or with a (combined) lifestyle intervention (RR 0.94; 95% CI 0.76-1.18; I^2 0%; Supplementary Figure S3). Meta-regression showed no influence of duration of intervention (beta 0.00, p-value 0.67), mean age at baseline (beta 0.00, p-value 0.90), or contrast in SBP at follow-up between the intervention and control group (beta -0.01, p-value 0.30) (Figure 4). Also mean SBP at baseline or follow-up or decline in SBP during follow-up in the intervention group did not influence the result (Supplementary Figure S4). Pairwise meta-analyses showed no beneficial effect of specific classes of antihypertensive medication (Supplementary Table S3), apart from the result of the Syst-Eur trial (RR 0.47; 95% CI 0.28-0.78), which was the only trial on the effect of calcium channel blockers.[44] In one trial that assessed a multi-domain intervention including lifestyle changes, a competing risk analysis was performed, showing no significant effect of the intervention on dementia or mortality.[16] In total, 2721 out of 32148 patients (8.5%) died in the intervention group and 2863 out of 31797 (9.0%) in the control group, which resulted in a RR on mortality of 0.93 (95% CI 0.87-0.99; I^2 31%; Supplementary Figure S5).

DISCUSSION

Our meta-analysis could not confirm that lowering BP with medication and/or lifestyle changes leads to a significant reduction of incident all-cause dementia, Alzheimer's disease or vascular dementia. The results were not significantly influenced by the presence of a history of stroke, diabetes, age, duration of the intervention or SBP. Only one trial performed a competing risk analysis.

Our neutral result is in line with two previous systematic reviews; broadening the scope to primary and secondary cardiovascular prevention, and including lifestyle changes in addition to use of antihypertensive medication, did not have any apparent effect on

the overall estimate.[21,33] Nevertheless, all three point estimates of the meta-analyses are consistently in favour of strategies aimed at BP-lowering. Our update of the literature, and thereby increased number of participants, reduces the likelihood that the absence of a significant effect is due to a power problem.

The present findings may be explained by the fact that participants in the included trials had a mean age of 64-84 years, while the strong association between a high BP and the risk of dementia is mainly evident from observational studies with hypertension at midlife (35-64 years).[10] Whether BP-lowering at midlife can prevent dementia later in life is difficult to demonstrate unequivocally, due to the long time lag between risk exposure and treatment on the one hand and disease occurrence on the other. It would be valuable if RCTs with BP-lowering interventions in this age group were to include an observational extended follow-up with dementia as outcome.[28] As hypertension is but one of many risk factors for all-cause dementia,[10] with a modest potential effect, it might be interesting to see if treatment of multiple risk factors alerts a more substantial risk reduction. Observational studies have suggested that in older adults a lower BP may even be harmful for cognitive function,[20] although there are no clinical trials to support this.[23] In our meta-regression analyses we did not find clues for a potentially harmful effect of BP-lowering at older ages or with lower SBP. It will be interesting to see if this is supported by the *Systolic Blood Pressure Intervention Trial memory and cognition in decreased hypertension* (SPRINT-MIND), a trial that compares intensive to standard BP control (target SBP of ≤120 versus ≤140 mmHg).[50] The results of this trial are, however, not likely to change the lack of beneficial effect we found in our meta-analysis (Supplementary Appendix S2).

The relatively short follow-up of most studies, is another potential explanation for the absence of a clear protective effect.[51] It can be argued that less than five years may be too short to assess the effect of BP-lowering on dementia, as it intervenes in a relative slow causal pathway with hypertension leading to atherosclerosis, cerebrovascular lesions and ultimately dementia.[51] Our meta-regression did not show a stronger effect in trials with a longer intervention duration. However, the two trials with an intervention duration >5 years were the two trials with a lifestyle or combined intervention and reached a relative small contrast in BP between the intervention and control group, which could have also limited their beneficial effect.[16,35] This limits our ability to conclude whether BP-lowering interventions are effective in reducing the risk of dementia on the long term.

Finally, the absence of a protective effect on incident dementia might be (partially) explained by the competing risk of death. The differential effect on mortality in the BP-lowering group, introduces an imbalance in the number of survivors who are still at risk of dementia and potentially also an age imbalance, while increasing age is the most important risk factor for dementia. Given the fact that the confidence interval only just overlapped one, even a small effect on mortality could have contributed to the overall neutral effect in our meta-analysis.

When analysing the results of an individual trial, it is possible to account for competing risks by performing a competing risk analysis.[52] However, in the included studies only one trial performed such an analysis, with, in contrast to the pooled effect, no significant effect on mortality.[16] Within a meta-analysis with aggregated data it is not yet possible to perform an accurate competing risk analysis. We could therefore not refute the possibility of a type II error due to competing risk of death.

An important strength of our systematic review is the large number of included participants, with data on almost 60 thousand participants including 2131 incident cases of dementia. Overall, our meta-analysis showed consistent results with low statistical heterogeneity and high level of evidence. It is relatively new to address the influence of competing risk of death in a systematic review of dementia prevention trials, which might be crucial to substantiate an effect. By including both interventions with antihypertensive medication as well as lifestyle changes, we assessed the effect of a wide range of BP reductions, which appeared to be lower in trials with lifestyle changes. This could also be interpreted as a limitation, because the anticipated effect on dementia risk reduction would be smaller with smaller BP reductions. However, our meta-regression did not show a significant effect of the degree of BP reduction. Another disadvantage of the inclusion of lifestyle interventions is that participants could not be blinded for the intervention, which could create a risk of performance bias. A second potential limitation is the large differences in study population across the trials, reflected in the wide variety in dementia incidence rates. Nonetheless, no apparent benefit or harm of specific population characteristics was apparent in our subgroup analyses, particularly not according to age, which is the most important driver for the wide range in dementia incidence rates.

To conclude, we could not show that BP-lowering interventions, including antihypertensive medication and/or lifestyle changes, in people over 60 years old reduce the risk of incident all-cause dementia. This appears independent of dementia subtype and the level of BP reduction. As few trials had an intervention duration longer than 5 years, a long-term effect could not yet be refuted. No trials assessing the effect of lowering BP on incident dementia were performed in midlife populations. A potential type II error due to the competing risk of death is conceivable and we recommend future RCTs to include such an analysis.

SUPPLEMENTARY MATERIAL

Appendix S1. Search strategy

(((((“Dementia”[Mesh] OR dement*[tiab] OR alzheimer*[tiab]))) AND ((((((“Antihypertensive Agents”[Mesh] OR “Antihypertensive Agents” [Pharmacological Action] OR “Hypertension/drug therapy”[Mesh] OR “Hypertension/prevention and control”[Mesh] OR “Hypertension/therapeutic use”[Mesh] OR “Hypertension/therapy”[Mesh] OR “Hypertension/diet therapy”[Mesh] OR “Hypertension/drug effects”[Mesh] OR “Nutrition Therapy”[Mesh] OR “Diet, Food, and Nutrition”[Mesh] OR “Diet”[Mesh] OR “Alcohol Drinking”[Mesh] OR “Exercise”[Mesh] OR “Exercise Therapy”[Mesh] OR “Exercise Movement Techniques”[Mesh] OR “Sports”[Mesh] OR “Physical Fitness”[Mesh] OR “Body Weight”[MeSH] OR “Life Style”[Mesh] OR “Tobacco Use”[Mesh] OR “Tobacco Use Cessation”[Mesh] OR “Smoking Cessation”[MeSH] OR exercis*[tiab] OR aerobic*[tiab] OR physical activit*[tiab] OR sport*[tiab] OR physical fitness*[tiab] OR diet*[tiab] OR nutrition*[tiab] OR nutrient*[tiab] OR food[tiab] OR feeding[tiab] OR weigh*[tiab] OR overweigh*[tiab] OR obes*[tiab] OR smok*[tiab] OR life style*[tiab] OR lifestyle*[tiab])))) OR (((pharmacolog*[tiab] OR nonpharmacolog*[tiab] OR non-pharmacolog*[tiab]) AND (intervention*[tiab] OR treatment*[tiab] OR therap*[tiab] OR management[tiab] OR strateg*[tiab]))))) OR ((“Sodium Potassium Chloride Symporter Inhibitors”[Mesh] OR “Sodium Potassium Chloride Symporter Inhibitors” [Pharmacological Action] OR “Bumetanide”[Mesh] OR “Ethacrynic Acid”[Mesh] OR “Furosemide”[Mesh] OR “torsemide” [Supplementary Concept] OR “Sodium Chloride Symporter Inhibitors”[Mesh] OR “Sodium Chloride Symporter Inhibitors” [Pharmacological Action] OR “Hydrochlorothiazide”[Mesh] OR “Chlorothiazide”[Mesh] OR “Bendroflumethiazide”[Mesh] OR “Xipamide”[Mesh] OR “Indapamide”[Mesh] OR “Chlorthalidone”[Mesh] OR “Metolazone”[Mesh] OR “Diuretics, Potassium Sparing”[Mesh] OR “Amiloride”[Mesh] OR “Triamterene”[Mesh] OR “Dihydropyridines”[Mesh] OR “Amlodipine”[Mesh] OR “cilnidipine” [Supplementary Concept] OR “Felodipine”[Mesh] OR “Isradipine”[Mesh] OR “lercanidipine” [Supplementary Concept] OR “Nicardipine”[Mesh] OR “Nifedipine”[Mesh] OR “Nimodipine”[Mesh] OR “Nitrendipine”[Mesh] OR “mepirodipine” [Supplementary Concept] OR “lacidipine” [Supplementary Concept] OR “aranidipine” [Supplementary Concept] OR “azelnidipine” [Supplementary Concept] OR “benidipine hydrochloride” [Supplementary Concept] OR “clevidipine” [Supplementary Concept] OR “darodipine” [Supplementary Concept] OR “efonidipine” [Supplementary Concept] OR “manidipine” [Supplementary Concept] OR “niguldipine” [Supplementary Concept] OR “nilvadipine” [Supplementary Concept] OR “Nisoldipine”[Mesh] OR “Nitrendipine”[Mesh] OR “oxodipine” [Supplementary Concept] OR “pranidipine” [Supplementary Concept] OR “Diltiazem”[Mesh] OR “Verapamil”[Mesh] OR “Angiotensin-Converting Enzyme Inhibitors”[Mesh] OR “Captopril”[Mesh] OR “Enalapril”[Mesh] OR “Fosinopril”[Mesh] OR “Lisinopril”[Mesh] OR “Perindopril”[Mesh] OR “quinapril” [Supplementary Concept] OR “Ramipril”[Mesh] OR “trandolapril” [Supplementary Concept] OR “benazepril” [Supplementary Concept] OR “zofenopril” [Supplementary Concept] OR “imidapril” [Supplementary Concept] OR “Cilazapril”[Mesh] OR “Angiotensin Receptor Antagonists”[Mesh] OR “candesartan” [Supplementary Concept] OR “eprosartan” [Supplementary Concept] OR “irbesartan” [Supplementary Concept] OR “Losartan”[Mesh] OR “olmesartan” [Supplementary Concept] OR “telmisartan” [Supplementary Concept] OR “Valsartan”[Mesh] OR “azilsartan” [Supplementary Concept] OR “fimasartan” [Supplementary Concept] OR “Atenolol”[Mesh] OR “Metoprolol”[Mesh] OR “Nadolol”[Mesh] OR “Nebivolol”[Mesh] OR “Oxprenolol”[Mesh] OR “Pindolol”[Mesh] OR “Propranolol”[Mesh] OR “Timolol”[Mesh] OR “Bisoprolol”[Mesh] OR “Acebutolol”[Mesh] OR

"Celiprolol"[Mesh] OR "esmolol" [Supplementary Concept] OR "Sotalol"[Mesh] OR "Doxazosin"[Mesh] OR "Phentolamine"[Mesh] OR "Indoramin"[Mesh] OR "Phenoxybenzamine"[Mesh] OR "Prazosin"[Mesh] OR "Terazosin" [Supplementary Concept] OR "Ketanserin"[Mesh] OR "urapidil" [Supplementary Concept] OR "Phentolamine"[Mesh] OR "carvedilol" [Supplementary Concept] OR "Labetalol"[Mesh] OR "Hydralazine"[Mesh] OR "Minoxidil"[Mesh] OR "aliskiren" [Supplementary Concept] OR "Mineralocorticoid Receptor Antagonists"[Mesh] OR "eplerenone" [Supplementary Concept] OR "Spironolactone"[Mesh] OR "Clonidine"[Mesh] OR "Guanabenz"[Mesh] OR "Guanfacine"[Mesh] OR "Methyldopa"[Mesh] OR "moxonidine" [Supplementary Concept] OR "Guanethidine"[Mesh] OR "Mecamylamine"[Mesh] OR "Magnesium Sulfate"[Mesh] OR antihypertensive[tiab] OR anti-hypertensive[tiab] OR beta-blocker*[tiab] OR betablocker*[tiab] OR angiotensin*[tiab] OR loop diuretic*[tiab] OR bumetanide[tiab] ethacrynic acid[tiab] OR furosemide[tiab] OR torsemide[tiab] OR thiazide diuretic*[tiab] OR epitizide[tiab] OR hydrochlorothiazide[tiab] OR chlorothiazide[tiab] OR bendroflumethiazide[tiab] OR xipamide[tiab] OR indapamide[tiab] OR chlorthalidone[tiab] OR metolazone[tiab] OR amiloride[tiab] OR triamterene[tiab] OR amlodipine[tiab] OR cilnidipine[tiab] OR felodipine[tiab] OR isradipine[tiab] OR lercanidipine[tiab] OR levamlodipine[tiab] OR nicardipine[tiab] OR nifedipine[tiab] OR nimodipine[tiab] OR nitrendipine[tiab] OR barnidipine[tiab] OR lacidipine[tiab] OR aranidipine[tiab] OR azelnidipine[tiab] OR benidipine[tiab] OR clevidipine[tiab] OR darodipine[tiab] OR efonidipine[tiab] OR manidipine[tiab] OR niguldipine[tiab] OR nilvadipine[tiab] OR nisoldipine[tiab] OR nitrendipine[tiab] OR oxodipine[tiab] OR pranidipine[tiab] OR diltiazem[tiab] OR verapamil[tiab] OR ACE-inhibitor*[tiab] OR captopril[tiab] OR enalapril[tiab] OR fosinopril[tiab] OR lisinopril[tiab] OR perindopril[tiab] OR quinapril[tiab] OR ramipril[tiab] OR trandolapril[tiab] OR benazepril[tiab] OR zofenopril[tiab] OR imidapril[tiab] OR cilazapril[tiab] OR candesartan[tiab] OR eprosartan[tiab] OR irbesartan[tiab] OR losartan[tiab] OR olmesartan[tiab] OR telmisartan[tiab] OR valsartan[tiab] OR azilsartan[tiab] OR fimasartan[tiab] OR atenolol[tiab] OR metoprolol[tiab] OR nadolol[tiab] OR nebivolol[tiab] OR oxprenolol[tiab] OR pindolol[tiab] OR propranolol[tiab] OR timolol[tiab] OR bisoprolol[tiab] OR acebutolol[tiab] OR celiprolol[tiab] OR esmolol[tiab] OR sotalol[tiab] OR doxazosin[tiab] OR phentolamine[tiab] OR indoramin[tiab] OR phenoxybenzamine[tiab] OR prazosin[tiab] OR terazosin[tiab] OR tolazolin[tiab] OR ketanserin[tiab] OR urapidil[tiab] OR fentolamin[tiab] OR carvedilol[tiab] OR labetalol[tiab] OR hydralazine[tiab] OR minoxidil[tiab] OR aliskiren[tiab] OR eplerenone[tiab] OR spironolactone[tiab] OR clonidine[tiab] OR guanabenz[tiab] OR guanfacine[tiab] OR methyldopa[tiab] OR moxonidine[tiab] OR guanethidine[tiab] OR mecamylamine[tiab] OR magnesium sulfate[tiab]))))) AND (("Blood Pressure"[Mesh] OR "Blood Pressure Determination"[Mesh] OR "Blood Flow Velocity"[Mesh] OR "Hypertension"[Mesh] OR "Cardiovascular Diseases"[Mesh] OR "Cardiovascular Physiological Processes"[Mesh] OR antihypertens*[tiab] OR anti-hypertens*[tiab] OR blood pressur*[tiab] OR systolic[tiab] OR diastolic[tiab] OR blood flow[tiab] OR (blood[tiab] AND lower*[tiab]) OR hypertens*[tiab] OR vascular[tiab] OR cardiovascular[tiab]))) AND ((("Randomized Controlled Trial" [Publication Type] OR "Random Allocation"[Mesh] OR "Double-Blind Method"[Mesh] OR "Single-Blind Method"[Mesh] OR "Placebos"[Mesh] OR "Meta-Analysis" [Publication Type] OR "Clinical Trials as Topic"[MeSH Terms] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trial" [Publication Type] OR random*[tiab] OR trial*[tiab] OR RCT[tiab] OR RCTs[tiab] OR systematic review[tiab] OR meta-anal*[tiab] OR metaanal*[tiab])))) NOT (("Animals"[Mesh] OR animal*[tiab] OR rat[tiab] OR rats[tiab] OR mouse[tiab] OR mice[tiab] OR dog[tiab] OR dogs[tiab]) NOT "Humans"[Mesh])

Appendix S2. Potential influence of SPRINT-MIND

Systolic Blood Pressure Intervention Trial memory and cognition in decreased hypertension (SPRINT-MIND) will study if intensive blood pressure lowering leads to a lower risk of dementia over five years follow-up.[50] As this is an important and influential trial, we wanted to assess its potential influence on our meta-analysis.

In the SPRINT trial 4678 participants were included in the control group and 4683 participants in the intervention group, with a mean age at baseline of 68 years. For this analysis we estimated an incidence rate of 10.3 cases per 1000 person years in the control group, which was found in the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) cohort aged 70-74 years.[53] This would result to an estimated 241 dementia cases in the control group. In this meta-analysis we included the nine studies included in our original meta-analysis and additionally included three hypothetical results of SPRINT-MIND trial. To assess the potential range in pooled estimates we used the following two hypothetical results: 50% and 0% risk reduction. This led to a range in pooled estimates from 0.84 (95% confidence interval [95% CI] 0.70-1.00, I^2 77%) with 50% risk reduction to 0.94 (95% CI 0.87-1.03, I^2 9%) with 0% risk reduction.

Table S1 - Cochrane risk of bias assessment

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
SHEP[43]	+	+	+	+	?	+	?
Syst-Eur[44]	+	+	+	+	+	+	+
SCOPE[45]	+	+	+	+	+	+	?
PROGRESS[46]	+	+	+	+	+	+	+
ADVANCE[47]	+	+	+	?	+	+	+
HYVET-COG[21]	+	+	+	+	+	+	+
PROFESS[48]	+	+	+	?	?	+	-
PreDIVA[16]	+	+	-	+	+	+	+
Look AHEAD[35]	+	+	-	+	+	+	+

The green plus-signs indicate a low risk of bias, the jelow question mark-signs indicate an unclear risk of bias, and the red minus-sign indicates a high risk of bias.

Table S2 - Dementia incidence rate

	Definition of dementia	Total no. dementia cases	Total study population (n=)	Age (years)[a]	Mean duration of follow-up (years)	No. dementia cases per 1000 participants, per year[b]
SHEP[43]	American Psychiatric Association criteria	81	4736	72	4.5	3.8
Syst-Eur[44]	DSM-III-R	64	2902	70	3.9	5.7
SCOPE[45]	Modified ICD-10 research criteria	119	4937	76	3.7	6.5
PROGRESS[46]	DSM IV	410	6105	64	3.9	17.2
ADVANCE[47]	DSM IV	76	11140	66	4.3	1.6
HYVET-COG[21]	DSM IV	263	3336	84	2.2	36.4
PROFESS[48]	Based on clinical impression (not further specified)	817	17270	66	2.4	19.4
PreDIVA[16]	DSM IV	233	3454	75	6.7	10.1
Look AHEAD[35]	Based on cognitive, functional and depression test scores and medical information	68	3802	70	11.4	1.6

[a] Mean age of intervention group. [b] The number of dementia cases per 1000 participants/year is calculated based on total dementia cases, study population and mean duration of follow-up when not reported. [c] Assessment based on cognitive, functional and depression test scores in combination with medical and health information.

Table S3 - Pairwise meta-analysis of specific classes of antihypertensive medication

	No. of trials	No. cases/ participants*	RR (95% CI)	p-value	I^2
Diuretics	2	163 / 4052	0.89 (0.72-1.09)	0.25	0%
Calcium channel blocker	1	21 / 1485	0.47 (0.28-0.78)	<0.01	N.A.**
Angiotensin receptor blocker	2	470 / 11101	1.01 (0.89-1.14)	0.88	0%
Ace-inhibitor and diuretic	2	232 / 8620	0.91 (0.77-1.09)	0.30	0%

** Number of cases represent the number of dementia cases and total number of participants in the intervention group. **Statistical heterogeneity could not be assessed on the analysis on calcium channel blockers as this was based on one trial. N.A. indicates not applicable.*

Table S4 - Funders of the included trials

Trial	Funder
SHEP[43]	The National Heart, Lung, and Blood Institute; the National Institute on Aging
Syst-Eur[44]	Bayer AG; Merck Sharpe; Dohme
SCOPE[45]	AstraZeneca
PROGRESS[46]	Servier; the Health Research Council of New Zealand; the National Health and Medical Research Council of Australia
ADVANCE[47]	Servier; National Health and Medical Research Council of Australia
HYVET-COG[21]	The British Heart Foundation; Servier; imperial college
PROFESS[48]	Boehringer Ingelheim; Bayer-Schering Pharma; GlaxoSmithKline
PreDIVA[16]	Dutch Ministry of Health, Welfare and Sport; Dutch Innovation Fund; Netherlands Organisation for Health Research and Development
Look AHEAD[35]	National Institutes of Health (and additional non-commercial funding)

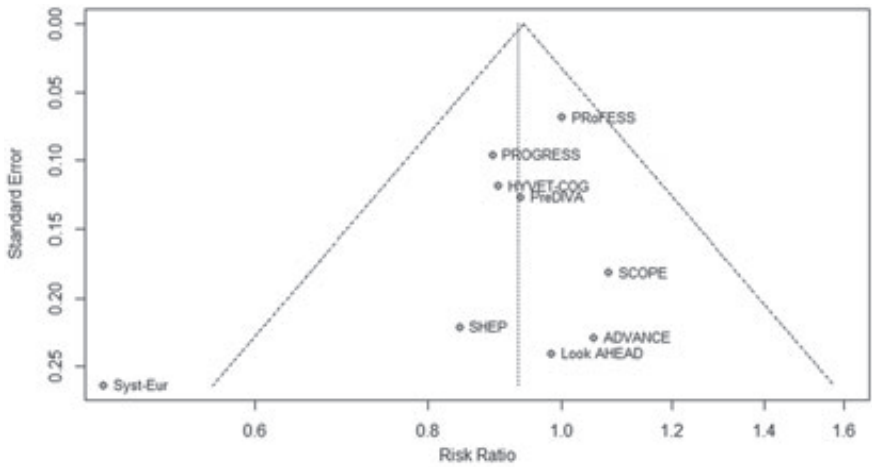

Figure S1 - Funnel plot to assess publication bias

Risk of publication bias is higher if the funnel plot is assymetrical. When for example smaller studies with non-significant effects are not published this will cause a gap in the bottom righ corner of the graph. Overall, we do not see a assymetrical funnel plot, however the outlying result from the Syst-Eur trial is notable.

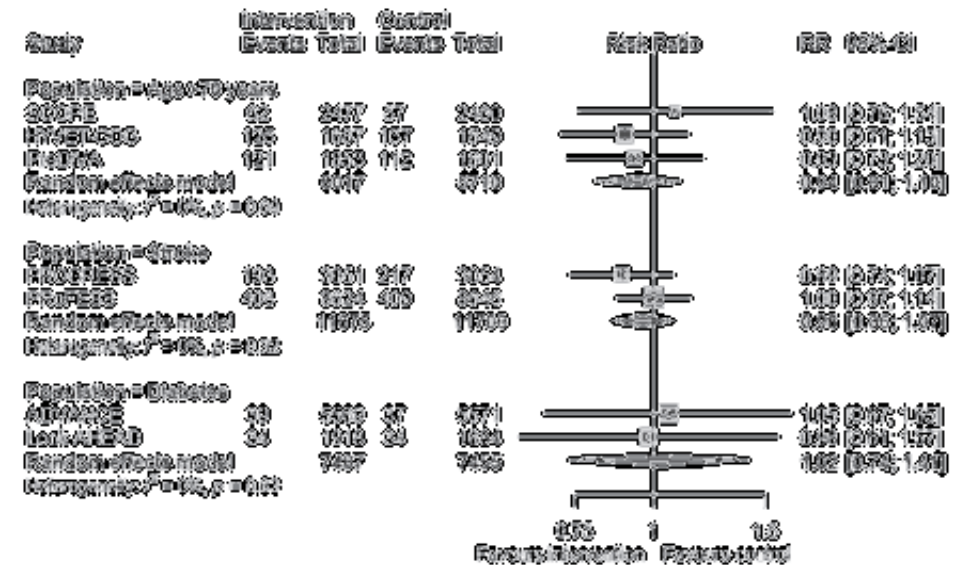

Figure S2 - Subgroup analyses on population characteristics

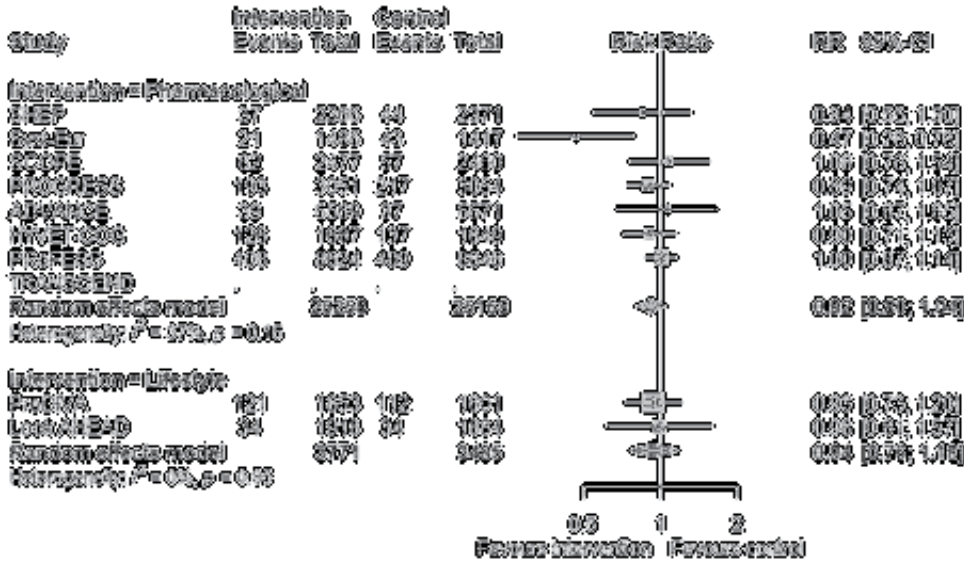

Figure S3 - Subgroup analyses on type of intervention

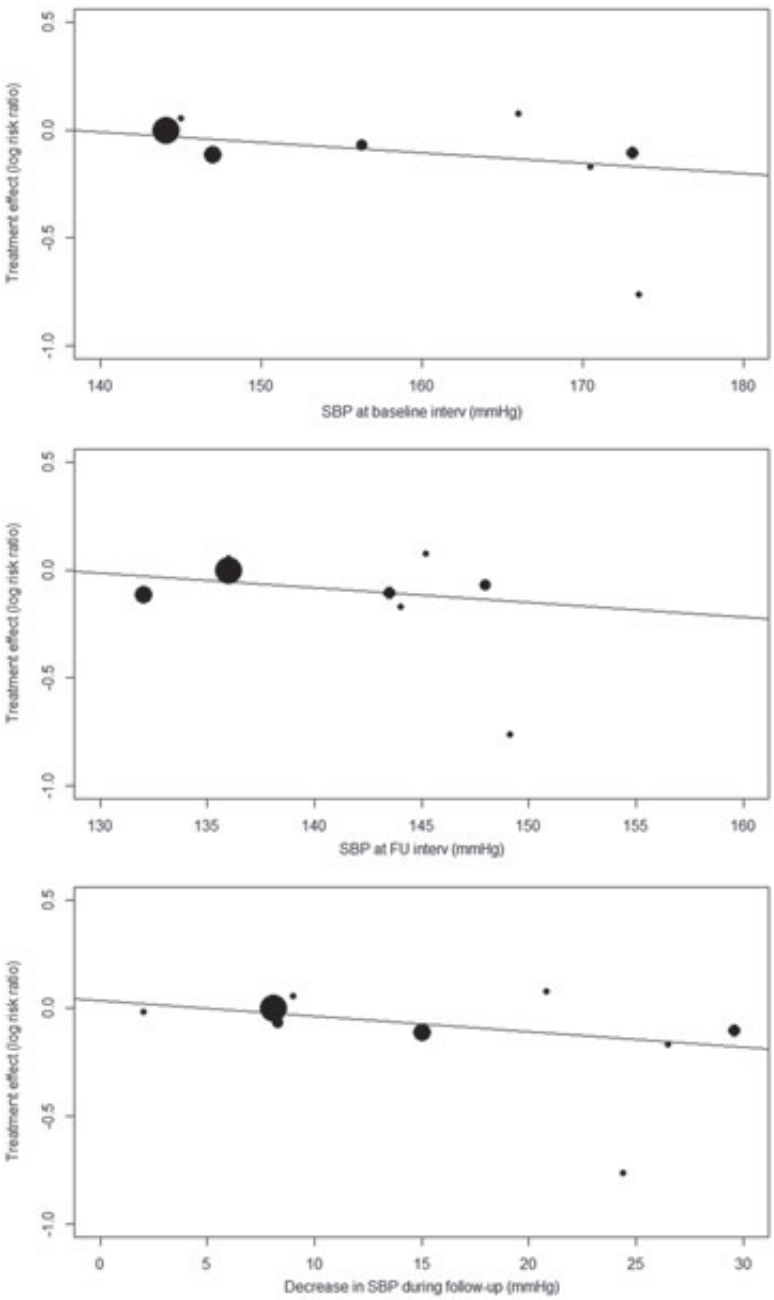

Figure S4 - Meta-regression assessing the influence of systolic blood pressure on the effect of blood pressure lowering treatment to prevent dementia

Data on SBP was gathered from the primary publication in the PRoFESS and PROGRESS trial.[54,55] SBP indicates systolic blood pressure; FU, follow-up.

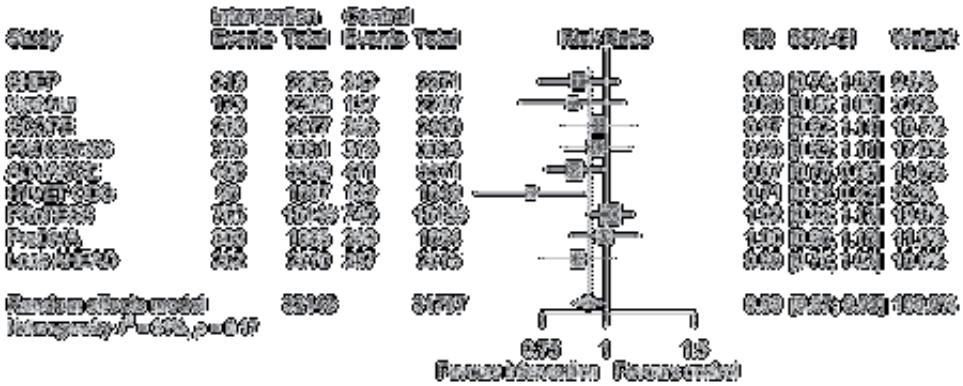

Figure S5 - Forest plot on the effect of antihypertensive treatment on mortality

LOWER DEMENTIA RISK WITH DIFFERENT CLASSES OF ANTIHYPERTENSIVE MEDICATION IN OLDER PATIENTS

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Lonneke A. van Vught
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3

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ABSTRACT

Objective Use of antihypertensive medication (AHM) is potentially associated with a reduced risk of dementia. Both calcium channel blockers (CCBs) and angiotensin receptor blockers (ARBs) are suggested to have a more pronounced protective effect. We aimed to study the association between different classes of AHM and dementia in older people.

Methods A subgroup of community-dwelling older people using AHM included in the 'Prevention of Dementia by Intensive Vascular Care' (preDIVA) randomized controlled trial was studied. Incident dementia rates in participants with different AHM classes (mono- and combination therapy) were compared to dementia rates in participants with any other AHM.

Results At baseline, 1951 participants (55.3%) used AHM (mean age, 74.4 year [SD 2.5]; mean systolic blood pressure, 156.4 mmHg [SD 21.5]). 986 participants (50.5%) used beta-blockers, 798 diuretics (40.9%), 623 angiotensin converting enzyme inhibitors (31.9%), 522 CCBs (26.8%), and 402 ARBs (20.6%). After 6.7 years (interquartile range 6.0-7.3) of follow-up, 136 participants (7.0%) developed dementia. Both use of CCBs (hazard ratio [HR] 0.56, 95% confidence interval [95% CI] 0.36-0.87) and ARBs (HR 0.60, 95% CI 0.37-0.98) were independently associated with a decreased risk of dementia. The association of CCBs with dementia was most apparent in participants without a history of cardiovascular disease (HR 0.38, 95% CI 0.18-0.81) and with uncontrolled hypertension (HR 0.26, 95% CI 0.11-0.61). Systolic blood pressure was not significantly lower in participants using CCBs or ARBs.

Conclusion Both use of CCBs and ARBs are independently associated with a decreased risk of dementia in older people.

INTRODUCTION

Dementia, to date, affects an estimated 36 million people worldwide.[56] Due to demographic changes this number will increase dramatically over the next decades.[56] Up to 30% of Alzheimer's disease is attributable to potentially modifiable, mostly vascular risk factors, with midlife hypertension accounting for 5%.[10] The high prevalence and readily available treatments render hypertension a suitable target for dementia prevention strategies.[57]

Despite the epidemiological evidence for hypertension as important risk factor for dementia, trials studying the effect of antihypertensive medication (AHM) on the incidence of dementia are inconclusive, showing small reductions at best.[21] Other mechanisms than blood pressure (BP) reduction alone might be responsible for part of the protective effect, explaining variability in effect from trials using different AHM classes.[22] Particularly, calcium channel blockers (CCBs) and angiotensin receptor blockers (ARBs) are suggested to have an additional protective effect on incident dementia.[22,58] This neuroprotective effect might be related to changes in Alzheimer's disease pathology, for example, plaques and tangles.[59] In observational studies, the protective effect of other AHM classes has also been suggested.[60] We aimed to study the association between different classes of AHM and incident, all-cause dementia in older people using AHM. We hypothesized an advantage of CCBs and ARBs additional to their BP-lowering effect.

METHODS

The current study is based on data from the 'Prevention of Dementia by Intensive Vascular care' trial.[61] In this multi-site, randomized controlled trial, 3526 community-dwelling older people aged 70-78 years received either intensive vascular care or standard care. During 6-8 years of follow-up the incidence of the primary endpoint of all-cause dementia was assessed. The trial was registered at International Standard Randomized Controlled Trial Number registry (ISRCTN29711771). The study protocol and primary outcome have been described in detail elsewhere.[61,62] The study was approved by the medical ethics committee of the Academic Medical Center and all participants gave written informed consent.

Data collection

At baseline and during follow-up, data on medication use and medical history was collected every 2 years with use of the electronic health records. We identified five different classes of AHM (β-blockers, diuretics, angiotensin converting enzyme (ACE) inhibitors, CCBs and ARBs) (supplementary Table 1). Data on education, smoking, and physical activity, defined according to WHO standards, were self-reported.[63] BP, body-mass index, and low-density lipoprotein cholesterol were measured using standardized protocols.[61] The mini-mental

state examination (MMSE) was used to measure cognition.[64] For the definition of dementia the criteria of the Diagnostic and Statistical Manual of Mental Disorders IV were used.[3] The diagnosis of dementia was evaluated by an independent outcome adjudication committee.[61] To minimise the risk of false-positive dementia diagnoses, all diagnoses were reevaluated with the treating physician after one year.[61]

Statistical analysis

All analyses were restricted to participants using AHM at baseline, to limit the influence of selective dropout that may have occurred after baseline. We compared use of the different AHM classes, including mono- and combination therapy, to any other AHM (without use of the class of interest during follow-up). A Cox proportional hazards regression model was used to analyse the association with dementia incidence rate. The number of days from baseline to the diagnosis of dementia, time of death, or final follow-up visit was used in the model. Crude analyses (model 1) were followed by analyses adjusted for history of cardiovascular disease (CVD; including myocardial infarction, stroke, and/or transient ischemic attack [TIA]) and type two diabetes mellitus (model 2), as these are guiding in clinical practice and were significantly different at baseline (Table 1).[65] In additional analyses we adjusted for randomization group and for the number of AHM classes to account for the severity of hypertension, as the Dutch cardiovascular risk management guideline recommends general practitioners to add multiple low-dose AHM classes when treatment effect is insufficient.[65] The proportional hazards assumption was tested visually and numerically, using Schoenfeld residuals.[66] The subclasses dihydropyridine and nondihydropyridine CCBs were individually assessed, as nondihydropyridine CCBs were previously identified as being associated with a reduced dementia risk.[67] To account for the overlap between different AHM classes, that is, participants that use multiple AHM classes, we combined all AHM classes into one model. As the diagnosis of dementia is often delayed [68] , we included an additional sensitivity analyses with a different operationalization of time-to-onset of dementia. The date of onset dementia was estimated by the midpoint between the last date seen well, defined as the last visit with a MMSE of at least 24, and the diagnosis of dementia. A competing risk analysis according to the cause-specific hazard method was used and the subdistribution hazard ratio was calculated, to account for the competing event of mortality before the possible development of dementia.[69] We performed subgroup analyses in participants with or without a history of CVD and with controlled or uncontrolled hypertension at baseline (defined as a systolic BP ≥155 mmHg; the median systolic BP at baseline), to assess the association in high versus low risk participants. A third subgroup analysis included participants with mono- or combination therapy. To assess whether participants with different AHM classes had a different BP at baseline and during follow-up, BP was compared using an independent *t*-test. Because few data were missing (supplementary Table 2), no

imputation was performed. We executed the analyses with R studio version 3.2, using the survival package.

RESULTS

In total, 1951 (55.3%) out of 3526 included participants used AHM at baseline [mean age, 74.4 year (SD 2.5)]. Mean systolic BP at baseline was 156.4 mmHg (SD 21.5). 906 (46.4%) participants used one class of AHM (monotherapy) (supplementary Table 3). Combining mono- and combination therapy, 986 participants (50.5%) used β-blockers, 798 diuretics (40.9%), 623 ACE-inhibitors (31.9%), 522 CCBs (26.8%), 402 ARBs (20.6%), and 32 other AHM (1.6%; Table1).

After a median of 6.7 years (interquartile range [IQR]; 6.0-7.3) of follow-up, 136 participants (7.0%) using AHM developed all-cause dementia. The incidence rate of dementia was 11.3 per 1000 person-years. Both the use of CCBs and ARBs was associated with a decreased risk of dementia compared to the use of other AHM [model 2; hazard ratio 0.56, 95% confidence interval (CI) 0.36-0.87; hazard ratio 0.60, 95% CI 0.37-0.98; respectively; Table 2 and Fig. 1a and 1b]. Comparable hazard ratios were found with additional adjustment for randomization group or for the number of AHM classes; however, in the latter the results were no longer significant (supplementary Table 4). The association with dementia was present in participants using dihydropyridine CCBs [*n*=17 dementia cases (4.3%); model 1; hazard ratio 0.49, 95% CI 0.29-0.82], but not in participants using nondihydropyridine CCBs [*n*=9 dementia cases (7.8%); model 1; hazard ratio 1.00, 95% CI 0.50-2.00]. The use of CCBs and/or ARBs at baseline was associated with a lower incidence of dementia (model 2; hazard ratio 0.48, 95% CI 0.33-0.71). Comparable results were found when combining all AHM classes into one model (supplementary Table 5). Also using time-to-onset defined as the date halfway between the last visit with a MMSE score of at least 24 and dementia gave comparable results (supplementary Table 6). When accounting for mortality (*n*=377) as competing event, CCBs and ARBs remained independently associated with a decreased risk of dementia (model 2; subdistribution hazard ratio 0.59, 95% CI 0.38-0.92; subdistribution hazard ratio 0.60, 95% CI 0.37-0.98; respectively; supplementary Table 7). In participants using ARBs, the association with dementia appeared comparable between the different subgroups, whereas in participants using CCB this was stronger in participants without a history of CVD (model 1; hazard ratio 0.38, 95% CI 0.18-0.81) and in participants with uncontrolled hypertension (model 1; hazard ratio 0.26, 95% CI 0.11-0.61; supplementary Table 7). Participants with uncontrolled hypertension were on average older (respectively, 74.5 and 74.2 year, P <0.01) and included fewer participants with a history of CVD (respectively, 43.0% and 55.6%, P <0.01). During follow-up BP was not significantly different for CCB or ARB users compared to other AHM, except for a lower diastolic BP at baseline in CCB users (supplementary Figure 1).

Table 1 - Baseline characteristics of participants with different classes of antihypertensive medication

		β-blocker		Diuretic		ACE-inhibitor		CCB		ARB	
		N= 986	P value	N=798	P value	N=611	P value	N=522	P value	N=402	P value
Sociodemographic											
Age (year)	Mean ± SD	74.3 ± 2.5	0.06	74.4 ± 2.5	0.29	74.4 ± 2.5	0.61	74.4 ± 2.5	0.84	74.2 ± 2.5	0.07
	Range	[69-80]		[69-79]		[69-80]		[69-80]		[69-80]	
Sex (male)	N (%)	478 (48.5)	0.02	312 (39.1)	<0.01	338 (55.3)	<0.01	245 (46.9)	0.92	175 (43.5)	0.14
Education (low)	N (%)	244 (24.7)	0.20	225 (28.2)	0.01	159 (26.0)	0.82	135 (25.9)	0.92	87 (21.6)	0.05
MMSE	Median [IQR]	28 [27-29]	0.44	29 [27-29]	0.63	28 [27-29]	0.01	29 [27-29]	0.09	29 [27-29]	<0.01
Blood pressure											
Systolic BP (mmHg)	Mean ± SD	156.8 ± 22.4	0.16	155.4 ± 21.5	0.61	156.5 ±22.1	0.35	155.9 ± 20.3	0.39	156.8 ± 23.1	0.22
	Range	[100.0-232.5]		[100.0-232.5]		[100.0-232.5]		[108.5–217.5]		[102.5-222.0]	
Diastolic BP (mmHg)	Mean ± SD	80.9 ± 11.4	0.12	80.9 ± 10.8	0.11	81.3 ± 11.9	0.89	79.5 ± 10.5	<0.01	81.5 ± 11.2	0.49
	Range	[50.0-131.0]		[52.0-119.0]		[52.0-131.0]		[52.0-124.5]		[55.0-117.5]	
Cardiovascular risk factors											
Cardiovascular disease*	N (%)	598 (60.6)	<0.01	369 (46.2)	0.05	312 (51.1)	0.30	293 (56.1)	<0.01	186 (46.3)	0.10
Diabetes mellitus	N (%)	248 (25.2)	0.45	238 (29.8)	<0.01	233 (38.1)	<0.01	156 (29.9)	0.01	112 (27.9)	0.34
Smoking (currently)	N (%)	123 (12.5)	1.00	92 (11.5)	0.30	79 (12.9)	0.50	66 (12.6)	0.57	44 (10.9)	0.40
Physically active	N (%)	820 (83.2)	0.17	642 (80.5)	0.08	485 (79.4)	0.02	421 (80.7)	0.28	330 (82.1)	1.00
LDL (mmol/L)	Mean ± SD	2.7 ± 0.9	<0.01	2.9 ± 1.0	0.49	2.8 ± 0.9	<0.01	2.8 ± 0.9	0.04	2.8 ± 1.0	0.46
BMI (kg/m^2)	Mean ± SD	28.3 ± 4.0	0.91	28.9 ± 4.5	<0.01	28.2 ± 4.1	0.72	28.4 ± 4.2	0.60	29.1 ± 4.6	<0.01

*Individual participants can be represented in different classes of AHM when they use combination therapy. Data are presented as numbers (percentage), mean (standard deviation [SD]), median (interquartile range [IQR]) or ranges. P values are calculated by comparing the AHM class of interest to any other AHM and are calculated with an independent T-test or Chi-squared test. *Cardiovascular disease includes myocardial infarction, stroke and/or TIA. ACE indicates angiotensin converting enzyme; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; MMSE, mini-mental state examination; BP, blood pressure; LDL, low-density lipoprotein; BMI, body-mass index.*

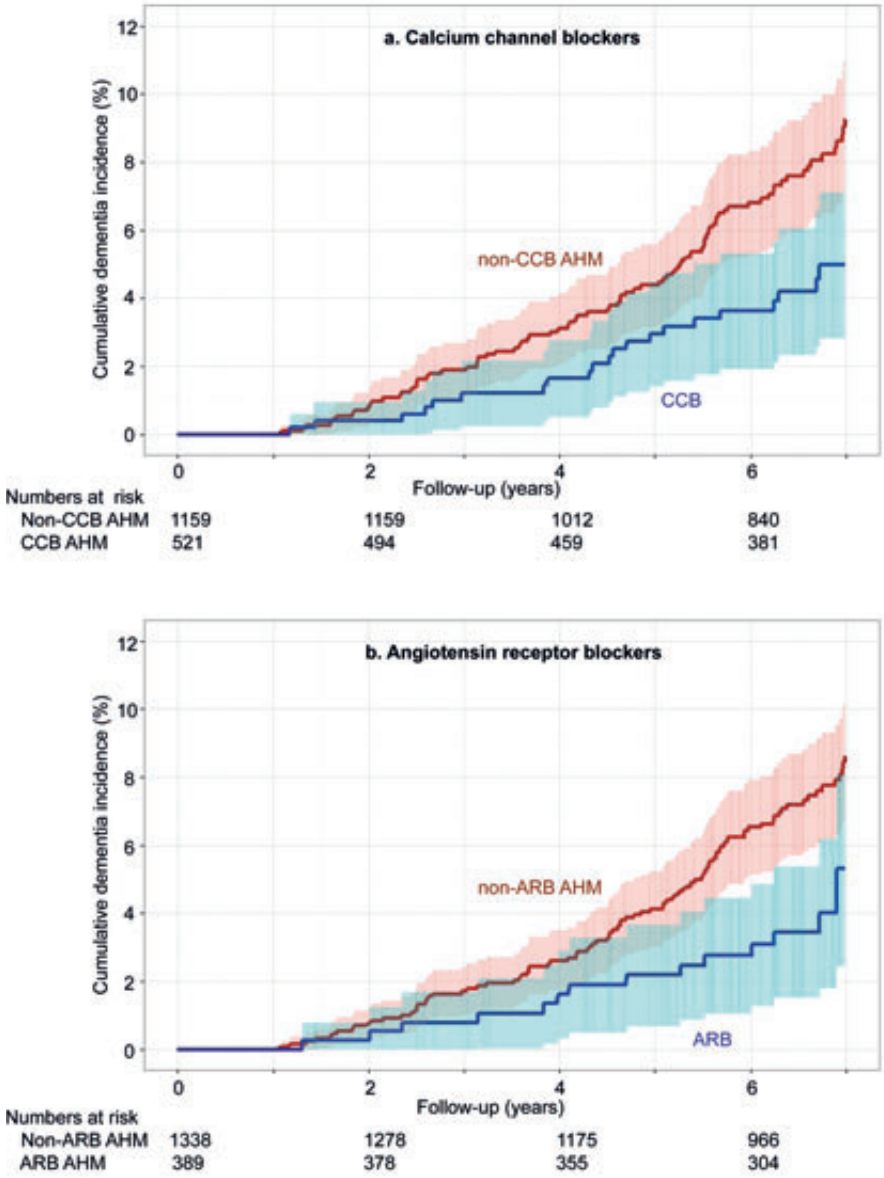


Figure 1 - Cumulative dementia incidence in participants using calcium channel blockers (A) or angiotensin receptor blocker (B) versus any other antihypertensive medication

Data are restricted to 7 year follow-up because of the low numbers of participants at risk of dementia in the 7-8 year follow-up period. CCB indicates calcium channel blockers; non-CCB AHM, any other antihypertensive medicine than a calcium channel blocker; ARB, angiotensin receptor blocker; non-ARB AHM, any other antihypertensive medicine than a angiotensin receptor blocker.

Table 2 - Cox proportional hazards regression comparing incident dementia rates in participant with different classes of antihypertensive medication (AHM) to participants with any other AHM

	Dementia cases (%)		Model 1		Model 2	
			HR	(95% CI)	HR	(95% CI)
β-blocker	69 / 963	(7.2%)	0.90	(0.63-1.29)	0.92	(0.64-1.32)
Diuretic	54 / 784	(6.9%)	0.82	(0.57-1.18)	0.81	(0.56-1.17)
ACE-inhibitor	43 / 600	(7.2%)	1.05	(0.72-1.51)	1.01	(0.69-1.48)
CCB	26 / 512	(5.1%)	0.56	(0.36-0.86)	0.56	(0.36-0.87)
ARB	20 / 389	(5.1%)	0.63	(0.39-1.02)	0.60	(0.37-0.98)

Model 1: unadjusted. Model 2: adjustment for history of cardiovascular disease and diabetes mellitus. The dementia cases (percentages) represent the number of participants with incident dementia from the participants using the AHM class of interest. HR indicates hazard ratio; CI, confidence interval; ACE, angiotensin converting enzyme; CCB, calcium channel blocker; ARB, angiotensin receptor blocker.

DISCUSSION

In this study, in patients using AHM, both the use of CCBs and ARBs was independently associated with a reduced risk of incident, all-cause dementia. The association was strongest for CCBs and in CCB users without a history of CVD or with uncontrolled hypertension.

In our study, 5.1% of participants using CCBs or ARBs developed dementia, in comparison to 6.7% (*n*=233) in the complete preDIVA study population (with and without AHM).[61] The association of CCBs and ARBs with a lower dementia incidence risk is in accordance with previous studies.[44,58] However, with regard to other AHM classes inconsistencies have been reported in observational studies, including a protective effect of diuretics and ACE inhibitors.[60] These discrepancies may be partially explained by variances in population and methodology, among others in comparator groups, that is, users of different classes of AHM versus nonusers, another AHM class or matched controls.[58] In our analysis, we chose to compare the AHM class of interest with any other AHM, as both groups are comparable with regard to their indication for AHM. In the future, AHM class preference might be aided by a possible effect on cognition.

No significant differences in BP were observed between the different AHM classes, except for a lower diastolic BP in participants with CCBs, suggesting that the protective effect is independent from the BP-lowering effect. There are several hypotheses about the neuroprotective effect of CCBs and ARBs. CCBs regulate calcium influx which may prevent neuronal cell death, inhibit the production of amyloid β and neurofibrillary tangles, and improve cerebrovascular perfusion by relaxing vascular smooth muscle cells.[59] Particularly dihydropyridine CCBs, which can effectively penetrate the blood-brain barrier, might be able to exert these direct effects on the brain.[70] The protective effect of ARBs might be related to improvement of the cerebral blood flow, restoration of cortical and cerebrovascular

angiotensin-1 and -4 receptors, decreased levels of amyloid β 1-42 in the brain, and an anti-inflammatory effect.[59]

We found a strong association between CCBs and dementia in participants without a history of CVD, a difference not previously studied in most trials or observational studies.[44,71] A possible explanation for this increased benefit in older people without a history of CVD could be related to less pronounced vascular lesions and, therefore, more brain reserve and capacity for functional resilience to cognitive decline. The additional benefit also appears to be more pronounced for participants with uncontrolled hypertension at baseline. The found association in participants with uncontrolled hypertension is supported by results from the 'Systolic Hypertension in Europe' trial, in which only patients with a systolic BP of at least 160 mmHg were included.[44] However, it might also have been influenced by a lower percentage of participants with a history of CVD. Owing to small numbers in the subgroup analyses, we could not adjust for this. The subgroup analysis suggests that CCBs have neuroprotective effects even when their BP lowering effect is inadequate. Our results from the subgroup analyses, however, should be interpreted with caution, as they are based on a small number of dementia cases.

Our study has strengths and limitations. An important limitation of our study is the fact that in clinical practice AHM is not prescribed at random, which may have led to confounding by indication. We adjusted for history of CVD and diabetes mellitus, but could not adjust for all possible confounders, due to a relative small number of dementia cases in each class of AHM. In 2006, Dutch guidelines recommended prescribing diuretics for patients without a history of CVD and β-blockers for patients with a history of myocardial infarction.[65] ACE inhibitors, ARBs, and CCBs were third choice AHM classes, for patients not responding sufficiently to diuretics and β-blockers. The association of ARBs and CCBs with a lower risk of dementia, might, therefore, be because of a selection of therapy-resistant patients with a high risk of CVD. However, the comparable results in the subgroup analysis comparing monotherapy with combination therapy mitigates this fear. The absolute number of dementia cases per AHM class was low limiting further analyses. Another limitation is the overlap between AHM classes, because many participants use multiple AHM classes. Nevertheless, the influence of this overlap on our primary analysis appeared limited, as comparable results were found in a sensitivity analysis in which all AHM classes were incorporated into one model. Information on medication history or dosage of AHM was not available, which prohibited further dose-response analyses. A strength of our study is the high follow-up rate (97.9%; *n*=1911), long follow-up period, and thorough outcome assessment, providing reliable information on incident dementia status.[61] Additionally, we studied a large sample of participants that is representative of the general Dutch population of 70-78 years using AHM.[72] Our annualized incidence rate of dementia was comparable to other studies with a similar study populations.[67,73] Finally, the analysis in which use of CCBs was combined with use of ARBs,

showed an even stronger association with dementia, indicating that the separate analyses may even be underestimations due to the presence of CCBs or ARBs in the comparator group. Further randomized controlled trials will be needed to provide clear answers about the effect of CCBs and/or ARBs on dementia.

In conclusion, both CCBs and ARBs are independently associated with a lower incidence of all-cause dementia compared with the use of other AHM. CCBs are associated with the lowest risk of dementia and this is mainly driven by dihydropyridine CCBs. Especially people without a history of CVD and with uncontrolled hypertension seem to benefit from CCB use.

SUPPLEMENTARY MATERIAL

Supplementary table 1 - A list of the different classes of antihypertensive medication and their ATC codes.

Class of antihypertensive medication	ATC codes
Beta-blockers	C07A, C07B, C07C, C07D, C07E, C07F
Diuretics	C03A, C03B, C03C, C03D, C03E, C03X
Angiotensin converting enzyme inhibitor	C09A, C09B
Calcium channel blocker	C08C, C08D, C08E, C08G
Angiotensin receptor blocker	C09C, C09D
Other	C02A, C02B, C02C, C02D, C02K, C02L, C02N, C09X

ATC indicates Anatomical Therapeutic Chemical.

Supplementary table 2 - Number of participants with missing data for each variable of interest.

Variables	Participants with missing data (number, %)	
Included in analyses		
Antihypertensive medication[a]	5	(0.1%)
Dementia	40	(2.1%)
History of CVD	24	(1.2%)
Diabetes mellitus	0	(0.0%)
Included in baseline table		
Age	0	(0.0%)
Gender	0	(0.0%)
Blood pressure	0	(0.0%)
Smoking	3	(0.2%)
Physical activity	41	(2.1%)
LDL	201	(10.3%)
BMI	1	(0.1%)

[a]*Percentage calculated is based on all participants included in the analyses (n=1951). CVD indicates cardiovascular disease; LDL, low-density lipoprotein; BMI, body-mass index.*

Supplementary table 3 - Medication use at baseline in participants with different classes of antihypertensive medication.

	Beta-blocker N= 986		Diuretic N=798		ACE-inhibitor N=611		CCB N=522		ARB N=402	
Number of AHM classes										
1	304	(30.8)	185	(23.2)	173	(28.3)	107	(20.5)	131	(32.6)
2	398	(40.4)	364	(45.6)	239	(39.1)	204	(39.1)	160	(39.8)
3	222	(22.5)	186	(23.3)	154	(25.2)	153	(29.3)	84	(20.9)
≥4	62	(6.3)	63	(7.9)	45	(7.4)	58	(11.1)	27	(6.7)
AHM classes										
Beta-blocker	986	(100)	367	(46.0)	256	(41.9)	231	(44.3)	156	(38.8)
Diuretics	367	(37.2)	798	(100)	245	(40.1)	173	(33.1)	124	(30.8)
ACE-inhibitor	256	(26.0)	245	(30.7)	611	(100)	163	(31.2)	14	(3.5)
CCB	231	(23.4)	173	(21.7)	158	(25.9)	522	(100)	109	(27.1)
ARB	156	(15.8)	124	(15.5)	14	(2.3)	109	(20.9)	402	(100)
Cholesterol lowering med.	541	(54.9)	364	(45.6)	347	(56.8)	207	(51.7)	188	(46.8)
Antithrombotic medication	589	(59.7)	354	(44.4)	323	(52.9)	285	(54.6)	179	(44.5)

Individual participants can be represented in different classes of AHM when they use combination therapy. Data are presented as numbers (percentage). ACE indicates angiotensin converting enzyme; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; AHM, antihypertensive medication; med., medication.

Supplementary table 4 - Analysis adjusted for randomisation group and the number of antihypertensive medication classes

	Model 2 + randomisation		Model 2 + nr. of AHM	
	HR	**(95% CI)**	**HR**	**(95% CI)**
Beta-blocker	0.91	(0.63-1.32)	1.12	(0.76-1.64)
Diuretic	0.81	(0.56-1.17)	1.03	(0.68-1.56)
ACE-inhibitor	1.01	(0.69-1.48)	1.16	(0.78-1.72)
CCB	0.56	(0.36-0.87)	0.65	(0.40-1.05)
ARB	0.60	(0.37-0.98)	0.66	(0.40-1.09)

Cox proportional hazards regression comparing incident dementia rates in participants with different classes of antihypertensive medication (AHM) to participants with any other AHM. Data are presented for model 2 (adjusted for history of cardiovascular disease and diabetes), with additional adjustment for randomisation group (intensive vascular care or standard care) and number of antihypertensive medicine classes. Nr. indicates number, AHM, antihypertensive medicine; HR, hazard ratio; CI, confidence interval; ACE, angiotensin converting enzyme; CCB, calcium channel blocker; ARB, angiotensin receptor blocker.

Supplementary table 5 - Sensitivity analysis including all antihypertensive medication classes in one model

	Model 1	
	HR	**(95% CI)**
Beta-blocker	0.89	(0.56-1.39)
Diuretic	0.72	(0.47-1.10)
ACE-inhibitor	0.87	(0.55-1.39)
CCB	0.54	(0.31-0.92)
ARB	0.54	(0.29-0.98)

Cox proportional hazards regression comparing incident dementia rates in participant with different classes of antihypertensive medication (AHM) (combined into one model). HR indicates hazard ratio; CI, confidence interval; ACE, angiotensin converting enzyme; CCB, calcium channel blocker; ARB, angiotensin receptor blocker.

Supplementary table 6 - Sensitivity analysis with an alternative operationalization of dementia onset

	Model 1		Model 2	
	HR	**(95% CI)**	**HR**	**(95% CI)**
Beta-blocker	0.92	(0.65-1.31)	0.95	(0.66-1.36)
Diuretic	0.89	(0.62-1.28)	0.87	(0.60-1.26)
ACE-inhibitor	1.04	(0.72-1.50)	0.99	(0.68-1.45)
CCB	0.58	(0.38-0.89)	0.58	(0.38-0.90)
ARB	0.63	(0.39-1.02)	0.59	(0.36-0.97)

Cox proportional hazards regression comparing time-to-onset of dementia in participants with different classes of antihypertensive medication (AHM) to participants with any other AHM. Time-to-onset of dementia is defined as the midpoint between the last visit with a MMSE ≥24 and the diagnosis of dementia. Model 1: unadjusted. Model 2: adjustment for history of cardiovascular disease and diabetes mellitus. HR indicates hazard ratio; CI, confidence interval; ACE, angiotensin converting enzyme; CCB, calcium channel blocker; ARB, angiotensin receptor blocker.

Supplementary table 7 - Competing risk analysis for the use of calcium channel blockers or angiotensin receptor blockers and dementia.

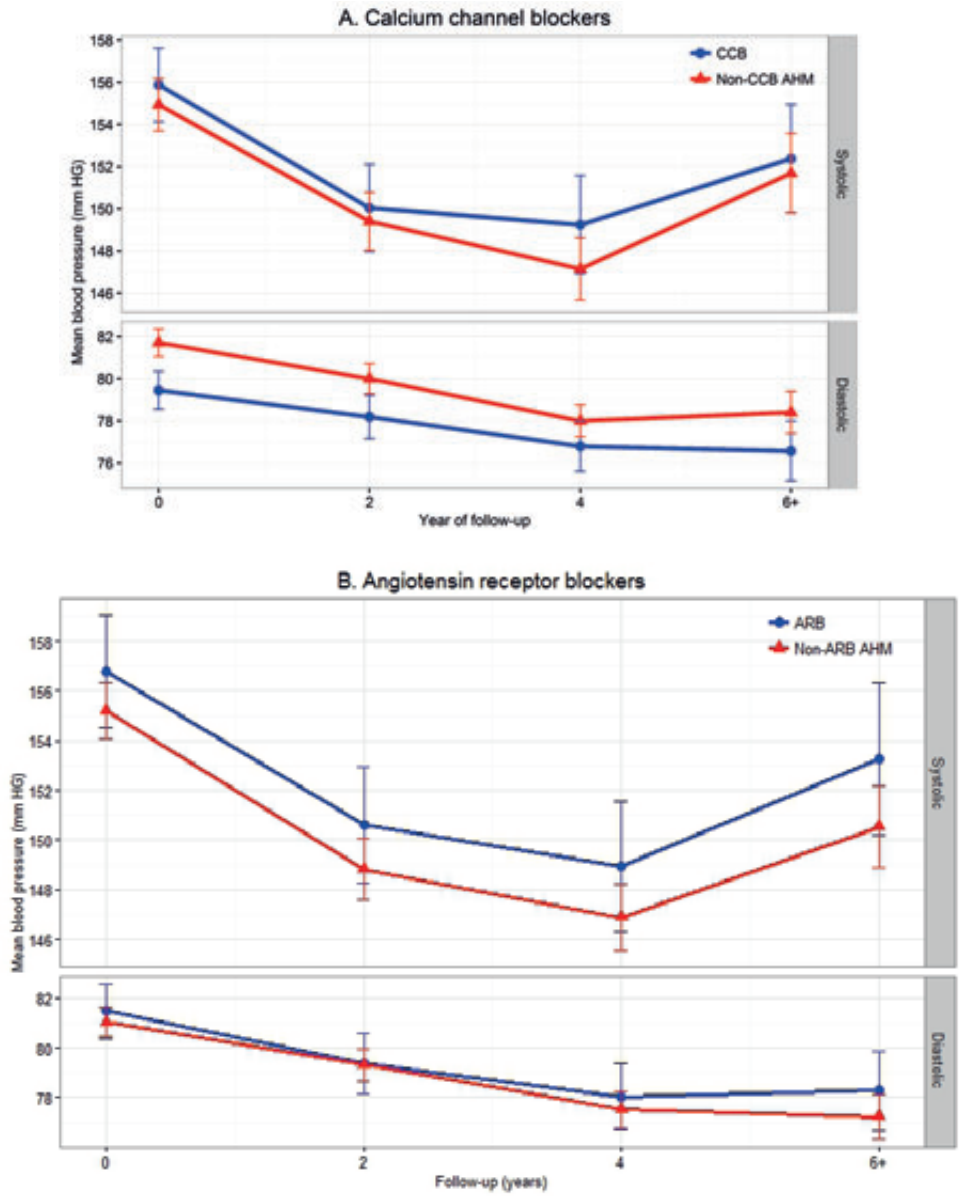
	Dementia-free survival CSHR (95% CI)	**Mortality CSHR (95% CI)**	**Dementia CSHR (95% CI)**	**Dementia SHR (95% CI)**
CCB	0.98 (0.87-1.10)	0.93 (0.73-1.18)	0.56 (0.36-0.87)	0.59 (0.38-0.92)
ARB	1.15 (1.01-1.31)	0.89 (0.68-1.16)	0.60 (0.37-0.98)	0.60 (0.37-0.98)

Analyses are adjusted for history of cardiovascular disease and diabetes mellitus (model 2). CSHR indicates cause specific hazard ratio, an estimate for the direct effect of CCB or ARB on survival, mortality or dementia. SHR indicates subdistribution hazard ratio, an estimate for the risk of dementia while accounting for mortality as competing event. CI indicates confidence interval; CCB, calcium channel blocker; ARB, angiotensin receptor blocker.

Supplementary table 8 - Subgroup analyses of the association between use of calcium channel blockers or angiotensin receptor blockers and dementia.

Subgroup analyses	Calcium channel blockers					Angiotensin receptor blockers				
	Dementia cases	(%)	HR	(95% CI)	P for interaction	Dementia cases	(%)	HR	(95% CI)	P for interaction
No history of CVD	9 / 220	(4.1%)	0.38	(0.18-0.81)	0.18	10 / 204	(4.9%)	0.58	(0.29-1.14)	0.85
History of CVD	17 / 287	(5.9%)	0.73	(0.41-1.27)		9 / 180	(5.0%)	0.63	(0.31-1.28)	
Uncontrolled hypertension	7 / 247	(2.8%)	0.26	(0.11-0.61)	0.03	10 / 191	(5.2%)	0.70	(0.35-1.38)	0.73
Controlled hypertension	19 / 265	(7.1%)	0.89	(0.52-1.52)		10 / 197	(5.1%)	0.61	(0.31-1.21)	
Monotherapy	6 / 106	(5.7%)	0.59	(0.25-1.36)	0.98	8 / 127	(6.3%)	0.68	(0.32-1.42)	0.99
Combination therapy	20 / 406	(4.9%)	0.59	(0.34-1.03)		12 / 262	(4.6%)	0.69	(0.36-1.30)	

The predefined subgroups are history of cardiovascular disease, (un)controlled hypertension (defined as systolic blood pressure ≥155 mmHg), and mono- or combination therapy. The P for interaction represents the p-value of the interaction term of the specific subgroup and CCBs/ARBs. Analyses are unadjusted (model 1) due to small numbers. The dementia cases (percentages) represent the number of participants with incident dementia from the participants using the AHM class of interest. HR indicates hazard ratio; CI, confidence interval; CVD, cardiovascular disease.



Supplementary figure 1 - Blood pressure during follow-up in participants using calcium channel blockers (A) or angiotensin receptor blockers (B).

Data is presented as mean (confidence interval). The blue line represents participants using calcium channel blockers (A) or angiotensin-2 receptor blockers (B). The red line represents participants using any other antihypertensive medication. CCB indicates calcium channel blockers; non-CCB AHM, any other antihypertensive medicine than a calcium channel blocker; ARB, angiotensin-2 receptor blocker; non-ARB AHM, any other antihypertensive medicine than a angiotensin-2 receptor blocker.

VISIT-TO-VISIT BLOOD PRESSURE VARIABILITY AND THE RISK OF DEMENTIA IN OLDER PEOPLE

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ABSTRACT

Background High visit-to-visit variability (VVV) in blood pressure (BP) is associated with cerebrovascular lesions on neuroimaging.

Objectives Our primary objective was to investigate whether VVV is associated with incident all-cause dementia. As a secondary objective, we studied the association of VVV with cognitive decline and cardiovascular disease (CVD).

Methods We included community-dwelling people (age 70-78 year) from the 'Prevention of Dementia by Intensive Vascular Care' (preDIVA) trial with three to five 2-yearly blood pressure measurements during 6-8 years follow-up. VVV was defined using coefficient of variation (CV; SD/mean × 100). Cognitive decline was assessed using the Mini-Mental State Examination (MMSE). Incident CVD was defined as myocardial infarction or stroke. We used a Cox proportional hazard regression and mixed-effects model adjusted for sociodemographic factors and cardiovascular risk factors.

Results In 2305 participants (aged 74.2±2.5) mean systolic BP over all available visits was 150.1 mmHg (SD 13.6), yielding a CV of 9.0. After 6.4 years (SD 0.8) follow-up, 110 (4.8%) participants developed dementia and 140 (6.1%) CVD. Higher VVV was not associated with increased risk of dementia (hazard ratio [HR] 1.00 per point CV increase; 95% confidence interval [CI] 0.96-1.05), although the highest quartile of VVV was associated with stronger decline in MMSE (β -0.09, 95% CI -0.17 to -0.01). Higher VVV was associated with incident CVD (HR 1.07; 95% CI 1.04-1.11).

Conclusion In our study among older people, high VVV is not associated with incident all-cause dementia. It is associated with decline in MMSE and incident CVD.

INTRODUCTION

Blood pressure (BP) and dementia are intricately linked. At older age, both a high systolic BP (SBP), low diastolic BP (DBP) and decreasing BP over time appear to be associated with an increased risk for dementia.[74,75] Recent studies have suggested that a high visit-to-visit variability (VVV) in BP might also be associated with an increased risk of cognitive decline and dementia.[76-78] BP variability can be measured over a short period (minutes to hours) or with longer intervals, i.e., visit-to-visit.[76] VVV is a relative new construct that is often available in clinical practice. It is associated with an increased risk of cardiovascular disease (CVD) and mortality possibly due to increased arterial stiffness and/or poor adherence to antihypertensive treatment causing both a high VVV and an increased risk of CVD.[27] The increased occurrence of cerebrovascular lesions on neuroimaging in persons with high VVV might contribute to decreased cognitive functioning and ultimately dementia.[76,78,79] The association between VVV and cognitive impairment has been established in several studies.[26,77] Until now only one study assessed the association with incident dementia and found a positive association.[78]

In this study we investigated whether VVV is associated with an increased risk of all-cause dementia in community-dwelling older people. Secondarily we assessed the association of VVV with cognitive decline and CVD.

METHODS

Study population and procedures

We performed our *post-hoc* analyses on data from the 'Prevention of Dementia by Intensive Vascular Care' (preDIVA) trial (ISRCTN29711771).[61] In short, this was a multisite, cluster-randomized, open-label trial on the effect of intensive vascular care on incident dementia. The intervention consisted of four-monthly visits to a practice nurse. During these visits, cardiovascular risk factors were assessed and lifestyle advice and drug treatment was provided conforming to national guidelines. The guidelines did not include management of VVV. Participants in the control condition received care as usual. For the current analyses, we considered the trial population as a single-cohort. All community-dwelling older people (aged 70 to 78 years) registered to the participating primary care practices, were invited to participate.[62] The only exclusion criteria were a diagnosis of dementia or a disorder likely to hinder successful long-term follow-up. Intervention and follow-up were 6-8 years. The medical ethics committee of the Academic Medical Center (AMC) in Amsterdam approved the study and all participants gave written informed consent.

At baseline and after two, four, and six years, all participants visited the study nurse for an in-person assessment during which BP and other values were measured. Participants recruited

early in the trial had a fifth visit after 7-8 years follow-up.[61] Only participants who completed three or more visits were included in the current analyses, as BP measurements at three separate visits were deemed as a minimum requirement for reliable determination of VVV. The BP measurements were performed in sitting position, using an automated BP monitor (M6, OMRON Healthcare Co., Ltd., Kyoto, Japan).[80] BP was measured twice at the same arm during each visit. For each visit, the mean BP of the two measurements was calculated and per visit one BP value, i.e., the mean, was used to calculate VVV. Data on demographic characteristics, cardiovascular history, diabetes mellitus, medication use, and smoking habits were self-reported and cross-referenced with electronic health records. Weight and length were measured in order to calculate body mass index (BMI), and a blood-sample was obtained for measurement of the low-density lipoprotein (LDL) cholesterol.

Definition of visit-to-visit blood pressure variability

There are several measures for VVV, including Standard Deviation (SD), Coefficient of Variation (CV; calculated as SD divided by mean BP over all available visits, times 100), variation independent of mean (VIM; a transformation of SD uncorrelated to mean BP), average real variability (ARV; the average of absolute differences between successive measurements) and delta BP (maximum BP minus minimum BP) [81]. The main difference between these measures is the extent to which they depend on mean and absolute BP, and the influence of order of the BP measurements. For our analysis, we deemed CV most appropriate as our primary VVV parameter, as it is independent from mean BP and allows our results to be compared to other studies, which mostly used CV.[78,82] Secondary analyses were conducted using the other VVV measures. Our primary analyses were executed with VVV based on SBP, but in secondary analyses we used VVV based on DBP.[78,82] To assess the influence of minimum and maximum SBP we divided participants in four mutually exclusive categories: stable normotension (maximum ≤140 mmHg), episodic moderate hypertension (minimum SBP ≤140 mmHg and maximum SBP 140-179 mmHg), episodic severe hypertension (minimum SBP ≤140 mmHg and maximum SBP ≥180 mmHg), and stable hypertension (all SBP >140 mmHg).[82]

Outcomes

Participants were referred to their general practitioner to evaluate the possibility of a cognitive disorder in case of cognitive complaints, a decline in Mini-Mental State Examination (MMSE) of ≥3 points since baseline or ≥2 point since the preceding visit, or with a MMSE of ≤24.[61] In case participants dropped-out from the trial information was retrieved on dementia status by contacting the participant, a relative, or the general practitioner. The primary outcome measure all-cause dementia was diagnosed according to the criteria of the Diagnostic and

Statistical Manual of Mental Disorders IV (DSM-IV).[3] An independent outcome adjudication committee blinded to treatment allocation assessed all possible and probable dementia cases based on available clinical data. Diagnosis of dementia was re-evaluated after one year, to minimize the risk of false-positive diagnoses. The committee also classified dementia cases into Alzheimer's disease, vascular dementia, and other dementia types. Cognitive functioning was measured at each visit using the MMSE.[64] CVD was defined as incident myocardial infarction or stroke, and included both morbidity and mortality. CVD morbidity was self-reported, cross-referenced with electronic health records, and CVD mortality was based on data from death certificates. In the first four years of follow-up, TIA and stroke were collected as a combined outcome. Stroke diagnosed in the first four years was therefore not included in the analyses.

Statistical analysis

We assessed the association between VVV and dementia using a Cox proportional hazards regression model. The number of days from baseline to date of diagnosis, final follow-up visit, or time of death was used as timescale. VVV was assessed both as continuous variable and divided into quartiles to investigate a possible non-linear relationship. We first assessed the unadjusted association (model 1). In a second model we adjusted for sex, age, and low educational level defined as no education or primary education only. In model three, we additionally adjusted for obesity, defined as BMI ≥30 kg/m^2, LDL cholesterol, smoking, and diabetes mellitus. These covariates were considered potential confounders as they are known to be independently associated with an increased risk of dementia [10]. Data is presented based on model three, unless indicated otherwise. The proportional hazards assumption was assessed visually using log-minus-log plots and Schoenfeld residuals.[66] We analyzed the relation between VVV and changes in MMSE over time with a linear mixed-effects model. For this analysis, we used VVV divided into quartiles and the lowest quartile was used as reference group. Different models were fitted, but a mixed model with the VVV quartiles, time (visits), and their interaction as fixed effects was deemed most appropriate as we were interested in the association between VVV and changes in cognition over time. To assess the association of VVV, as continuous variable and divided into quartiles, with CVD, we used a Cox proportional hazards regression model. Because mortality is a competing risk for dementia and is associated with a high VVV, it could lead to a type II error with respect to a possible association between VVV and dementia. Therefore, we conducted a competing risk analysis according to the cause-specific hazard method and calculated the subdistribution hazard ratio (HR).[69] The following predefined subgroup analyses were performed, including intervention versus control group, antihypertensive medication use at baseline, change in antihypertensive medication use (i.e., started or stopped) during follow-up, history of CVD (including myocardial infarction and stroke) at baseline, and

number of BP measurements. To assess the influence of selective drop-out on our results, we repeated our analyses with VVV only based on the first three BP measurements. To assess whether an association between VVV and dementia might be affected by overall changes in BP, we additionally adjusted for the slope in SBP over all available visits.[83] To assess if the results of our analyses are indeed independent from hypertension at baseline (defined as SBP >140 mmHg, DBP >90 mmHg and/or use of antihypertensive medication) or mean SBP during follow-up, we additionally adjusted for these variables. In previous reports, adherence to antihypertensive treatment and seasonal change were identified to potentially influence VVV.[84] The association between these variables and VVV was assessed with unpaired t tests. Adherence to antihypertensive treatment was operationalised as self-reported full compliance with the prescribed medication regimen. Seasonal change was defined as at least two visits in different seasons. All statistical tests were two-sided with a p-value of <0.05 considered statistically significant. For the eight different VVV measures, a p-value of <0.006 was considered statistically significant after Bonferroni correction for multiple testing. Missing data were not imputed (Supplementary Material 1, for additional information on statistical analyses). Analyses were done using the Statistical Package for Social Sciences version 24.0 (SPSS Inc., Chicago IL, USA) and R studio version 3.3.3.[42]

RESULTS

From the 3526 participants at baseline, 2305 attended three or more visits and could be included in the analyses (Figure 1, the compact version of the flow-diagram; Supplementary Figure 1, the complete flow-diagram). Baseline characteristics are shown in Table 1. Participants included in the analyses (i.e., those attending three to five visits) were slightly younger, had a lower SBP, less often a history of CVD, and had a higher MMSE at baseline compared to participants excluded from the analyses (Supplementary Table 1).

Mean SBP was 154.7 mmHg (SD 20.8) at baseline and 150.6 mmHg (SD 20.9) at the final follow-up visit (Supplementary Figure 2). Mean DBP was 81.3 mmHg (SD 10.6) at baseline and 77.3 mmHg (SD 11.3) at final follow-up. Mean CV of SBP was 9.0 (13.6 [SD] / 150.1 [mean] × 100) (Supplementary Table 2). As an example of the level of variability in SBP over time, we show the course in absolute SBP of four arbitrarily chosen participants representing the four quartiles of VVV (Supplementary Figure 3).

After an average follow-up of 6.4 years (SD 0.8), 110 participants (4.8%) were diagnosed with dementia (incidence rate: 7.0 per 1000 person-years). Of these, 82 (75%) had Alzheimer's disease, six (5%) vascular dementia, five (5%) dementia from another aetiology, and in 17 participants the type of dementia could not be classified. A higher CV of SBP was not associated with an increased risk of all-cause dementia (HR 1.00 per one point increase in CV of SBP, 95% confidence interval [CI] 0.96-1.05) (Table 2). No association with dementia risk and

other VVV parameters were found (Supplementary Table 2). Also when stratified according to different BP categories, there was no association with dementia (Supplementary Table 3). VVV divided into quartiles did also not reveal a non-linear association with dementia (Figure 2A). The number of dementia cases was 30 (5.5%) in the lowest quartile of VVV, 19 (3.3%, HR 0.6, 95% CI 0.3-1.1) in the second quartile, 32 (5.5%, HR 1.0, 95% CI 0.6-1.6) in the third quartile, and 29 (5.0%, HR 0.9, 95% CI 0.5-1.5) in the highest quartile. A higher CV of SBP was not associated with Alzheimer's disease (HR 1.00, 95% 0.96-1.06).

The MMSE of participants in the highest quartile of VVV (range CV of SBP 11.3-36.0) was 0.18 (95% CI 0.00 to 0.36) points lower at baseline and declined on average with 0.09 (95% CI 0.01 to 0.17) points per visit more than participants in the lowest quartile of VVV (range CV of SBP 0.4-5.9) (Supplementary Table 4). During follow-up CVD occurred in 140 participants (6.1%), of which 93 had a myocardial infarction and 47 a stroke. A higher CV of SBP was significantly associated with more incident CVD (HR 1.07; 95% CI 1.04-1.11) (Table 2) and VVV divided into quartiles showed a linear association (Figure 2B). Separate analyses yielded comparable results for myocardial infarction (HR 1.07; 95% CI 1.03-1.12) and stroke (HR 1.08; 95% CI 1.03-1.14).

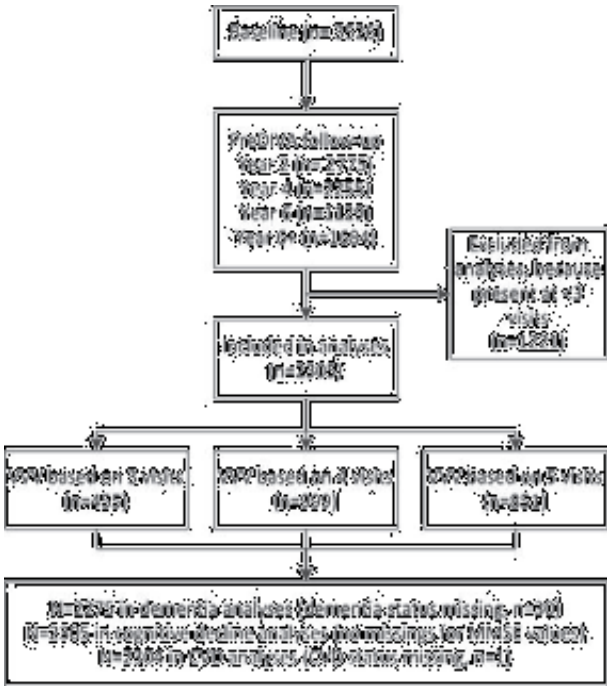


Figure 1 - Flow-diagram of the number of participants in- and excluded from the analyses.

Participants were included in the analyses if they had a valid blood pressure measurement at ≥3 visits. N, number of participants; VVV, visit-to-visit variability; MMSE, Mini-Mental State Examination; CVD, cardiovascular disease.

Table 1 - Baseline characteristics of participants who did or did not develop dementia

	All participants (n=2305)		Dementia (n=110)		No dementia (n=2165)		P value
Sex (male)	1032	(44.8%)	52	(47.3%)	58	(52.7%)	0.59
Age (y)	74.2	(2.5)	74.7	(2.5)	74.1	(2.4)	0.02
Ethnicity (Caucasian)	2191	(96.5%)	105	(96.3%)	2057	(96.5%)	0.86
Education (low)*	493	(21.6%)	32	(29.9%)	453	(21.1%)	0.03
History of CVD	756	(33.0%)	44	(40.0%)	696	(32.4%)	0.10
Diabetes mellitus	437	(19.0%)	29	(26.4%)	403	(18.6%)	0.04
Antiglycemic med.	326	(14.1%)	21	(19.1%)	302	(13.9%)	0.17
Hypertension**	2049	(88.9%)	97	(88.2%)	1923	(88.8%)	0.90
Antihypertensive med.	1246	(54.1%)	66	(60.0%)	1160	(53.6%)	0.19
Systolic BP (mmHg)	154.7	(20.8)	156.1	(21.5)	154.7	(20.8)	0.50
Diastolic BP (mmHg)	81.3	(10.6)	81.5	(11.2)	81.3	(10.6)	0.85
BMI (kg/m^2)	27.5	(4.2)	27.6	(4.0)	27.5	(4.1)	0.71
LDL cholesterol (mmol/L)	3.1	(1.0)	3.0	(1.0)	3.1	(1.0)	0.07
Cholesterol lowering med.	774	(33.6%)	39	(35.5%)	728	(33.7%)	0.78
Current smoker	279	(12.1%)	14	(12.7%)	258	(11.9%)	0.81
MMSE	29	[28-30]	28	[26-29]	29	[28-30]	<0.01
Intervention group	1233	(53.5%)	43	(39.1%)	1010	(46.7%)	0.12

*Baseline characteristics of all participants included in the analyses (i.e., present at ≥3 visits). Data are presented as frequencies (%), mean (SD) or median [interquartile range]. P values are calculated with a Chi-squared test, an unpaired T test or Mann-Whitney U test. * Low educational level defined as no education or primary education only. **Hypertension was defined as a systolic blood pressure at baseline ≥140 mmHg, a diastolic blood pressure at baseline ≥90 mmHg or the use of antihypertensive medication. CVD, cardiovascular disease; med., medication; BP, blood pressure; BMI, body mass index; LDL, low-density lipoprotein; MMSE, Mini-Mental State Examination.*

Table 2 - Cox proportional hazards regression on the association between blood pressure variability and dementia or cardiovascular disease.

	Dementia			Cardiovascular disease		
	Hazard ratio	**(95% CI)**	**P value**	**Hazard ratio**	**(95% CI)**	**P value**
Model 1	1.00	(0.96-1.04)	0.97	1.08	(1.04-1.11)	<0.01
Model 2	1.00	(0.96-1.05)	0.90	1.08	(1.04-1.11)	<0.01
Model 3	1.00	(0.96-1.05)	0.58	1.07	(1.04-1.11)	<0.01

Cardiovascular disease includes myocardial infarction or stroke. Model 1 is the unadjusted model; in model 2 we adjusted for gender, age, and low educational level; and in model 3 we additionally adjusted for obesity, low-density-lipoprotein, smoking and diabetes. CI indicates confidence interval.

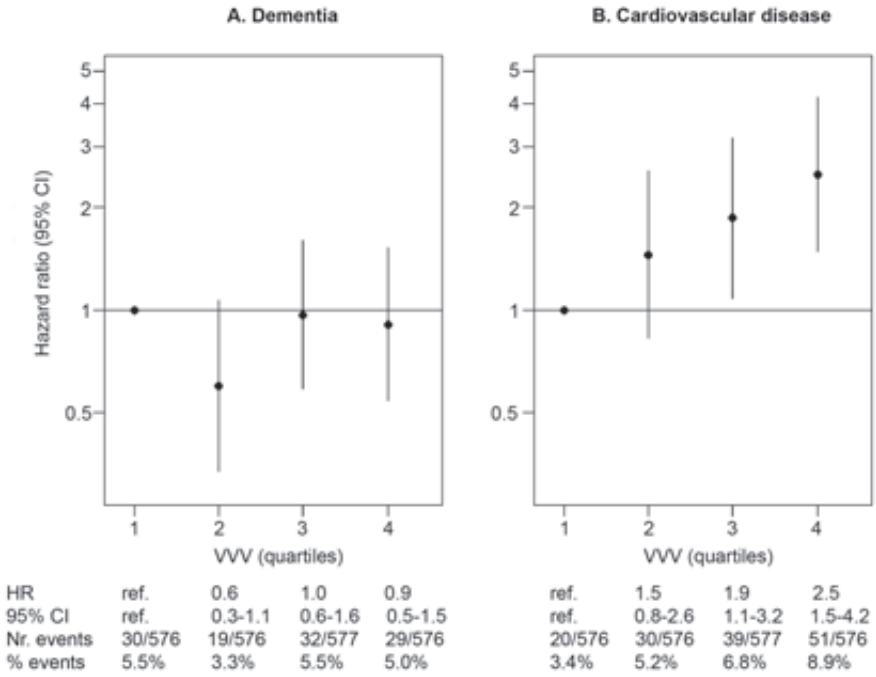


Figure 2 - Hazard ratios of the association between quartiles of coefficient of variation of systolic blood pressure and dementia (A) or cardiovascular disease (B).

Analyses are unadjusted. The y-axis is shown in logarithmic scale. Quartile 1 includes CV of SBP 0.4 to 5.9; quartile 2, CV of SBP 5.9 to 8.4; quartile 3, CV of SBP 8.4 to 11.3; quartile 4, CV of SBP 11.3 to 36.0. At the bottom of each graph, the number of participants with dementia or cardiovascular disease are shown in relation to the total number of participants per quartile. CI, confidence interval; VVV, visit-to-visit variability; CV, coefficient of variation; SBP, systolic blood pressure; HR, hazard ratio; ref., reference group.

Sensitivity analysis showed that there was no association between VVV and dementia when taking mortality into account in the competing risk analysis (subdistribution HR 1.01; 95% CI 0.96-1.05) (Supplementary Table 5). The predefined subgroup analyses yielded no apparent associations either (Table 3). No association with dementia was apparent when only including the first three BP measurements in the VVV measure (HR 1.01, 95% CI 0.97-1.05). Additional adjustment for trend in BP (HR 0.95, 95% CI 0.90-1.00, P=0.06), hypertension at baseline (HR 1.01, 95% CI 0.96-1.05) or mean SBP during follow-up (HR 1.01, 95% CI 0.96-1.05) did not change the association with dementia. Adherence to antihypertensive treatment did not significantly influence CV of SBP (adherent, n=1563, mean 9.3, SD 4.6; non-adherent, n=92, mean 9.2, SD 4.6; P=0.83), nor did seasonal change (BP measured in different seasons, n=615, mean 9.0, SD 4.4; BP measured in the same season, n=1690, mean 9.1, SD 4.5; P=0.64).

Table 3 - Subgroup analyses of the association between blood pressure variability and dementia.

	Dementia cases	(n=, %)	CV	(mean, SD)	HR (95% CI)	P value
Intervention group	67 / 1222	(5.5%)	9.3	(4.5)	0.98 (0.91-1.06)	0.66
Control group	43 / 1053	(4.1%)	8.8	(4.3)	1.01 (0.96-1.06)	0.81
AHM at baseline	66 / 1160	(5.4%)	9.4	(4.5)	1.04 (0.97-1.11)	0.30
No AHM at baseline	44 / 1047	(4.2%)	8.6	(4.3)	0.97 (0.92-1.03)	0.36
AHM started/stopped*	32 / 579	(5.5%)	9.7	(4.7)	0.99 (0.94-1.04)	0.70
No AHM started/stopped**	78 / 1696	(4.6%)	8.8	(4.3)	1.02 (0.95-1.10)	0.58
History of CVD	44 / 740	(5.9%)	9.4	(4.8)	0.93 (0.86-1.00)	0.05
No history of CVD	66 / 1520	(4.3%)	8.9	(4.3)	1.04 (0.99-1.10)	0.11
3 BP measurements	50 / 455	(11.0%)	8.4	(4.7)	1.01 (0.96-1.07)	0.86
4 BP measurements	43 / 999	(4.3%)	9.1	(4.7)	1.01 (0.95-1.07)	0.82
5 BP measurements	17 / 851	(2.0%)	9.4	(4.0)	1.06 (0.95-1.18)	0.35

*Analyses are unadjusted (model 1). *Antihypertensive medication started or stopped during follow-up. **Antihypertensive medication (yes or no) constant throughout study. Only the interaction term of 'history of CVD' and CV was significant (p=0.01). CV, coefficient of variation; SD, standard deviation; AHM, antihypertensive medication; CVD, cardiovascular disease (including myocardial infarction and stroke); CI, confidence interval.*

DISCUSSION

In our study population of community-dwelling older people, VV was not associated with incident, all-cause dementia after an average follow-up of 6.4 years. This result is irrespective of the measure of VV applied, mean SBP, use of antihypertensive medication, or history of CVD. High VV was associated with stronger decline in MMSE and with a higher incidence of CVD.

The absence of an association with dementia is in contrast with findings from the Three-City Study, in which a significant association between a higher VV and an increased risk of incident dementia was found.[78] This observational cohort study (n=6506 participants) is comparable regarding age, but had a lower systolic VV (CV of SBP, 7.2) and cardiovascular risk at baseline in comparison to our study population, with a lower mean SBP and fewer participants with diabetes mellitus. The calculation of VV and the follow-up duration was comparable to our analyses. In the Three-City study a higher incidence rate was found of 11.8 dementia cases per 1000 person-years, possibly due to a more sensitive dementia assessment procedure using a neuropsychological test battery as opposed to the pragmatic and clinical approach used in preDIVA. However, it seems unlikely that this influenced the association with VV. In a subgroup of our study population without a history of CVD, there was a trend towards a positive association between a higher VV and incident dementia, although this effect was small. Perhaps in older people with a higher cardiovascular burden, cerebrovascular damage, presumed to contribute to the occurrence of cognitive

decline and dementia, is already too advanced to detect a significant influence of VVV on incident dementia.[78,79] Another theoretical possibility explaining the contrast between our findings and those of the Three-City study is that our study was underpowered to detect an association. This seems unlikely since the HR for dementia was one; not suggestive of a small sample size as a cause of our null finding. Reproduction of these analyses in different study populations may be required to determine the true nature of the association between VVV and dementia incidence.

One of the hypotheses on a potential association between VVV and dementia is through progression of cerebrovascular lesions including white matter hyperintensities, cortical infarcts, and cerebral microbleeds.[77,79] We found an association between VVV and increased risk of stroke, and between VVV and decline in MMSE. It is conceivable that the 6-8 years of follow-up in our study was too short to detect a clinically overt effect on dementia incidence as a result of high VVV, or that at the age range in our study cerebrovascular damage has advanced too much for VVV to influence the progression. The relation between high VVV earlier in life (i.e., midlife or early late-life) and dementia in late life may be stronger, similar to the relation between absolute blood pressure in mid-life and dementia in late-life.[74] Other potential mechanisms underlying an association with dementia are that high VVV and cerebral amyloid-β depositions (an important neuropathological hallmark of Alzheimer's disease) are the result of increased arterial stiffness.[85] The neuropathological changes characteristic for Alzheimer's disease might also lead to autonomic dysfunction and through this a higher VVV, even before any cognitive problems have occurred.[26] Finally, a potential relation between VVV and dementia might not be causal, but both stem from a common underlying cause.

We found a significant association between VVV and decline in MMSE. This is in accordance with previous reports that found a positive association between VVV and cognitive deterioration.[26,77,86] However, the association found in our study is probably not clinically relevant, as it would take approximately 18 years for the MMSE to be one point lower in the highest versus the lowest VVV quartile. The MMSE is not very sensitive to minor cognitive changes and was developed as a screening tool for dementia.[64]

The association of VVV with CVD may have consequences for clinical practice. Potentially, antihypertensive treatment should not only be initiated and evaluated to reduce mean BP, but also to reduce VVV. The effect of different antihypertensive drugs on VVV is variable, and the lowest VVV is seen in treatment with calcium-channel blockers and non-loop diuretics.[87] The drug-class differences can partially account for the difference in stroke risk, but not for the difference in risk of myocardial infarction.[87] Interestingly, calcium channel blockers belong to the class of antihypertensive drugs associated with a lower risk of dementia.[41]

Strengths of our study are the large number of participants and virtually complete information on primary outcome. The assessment of dementia was thorough with a long follow-up and

validation by an independent outcome adjudication committee, since it concerned the primary outcome of the preDIVA study.[61] We added several sensitivity analyses, including other VVV measures, to strengthen our findings. An important limitation of our study is that the number of available BP measurements is limited and the interval between BP measurements is relatively long. Analyses stratified for number of BP measurements showed that participants with only three BP measurements had on average a lower VVV (CV 8.4) and a non-significantly higher risk of dementia (11%). To assess whether selective drop-out influenced our results, we repeated our analyses with VVV based only on the first three BP measurements, but this did not change the results. Some participants who were excluded from the analyses because of <3 BP measurements had an MMSE <24 at their last visit. Due to the limited number of BP measurements, we are unable to assess whether these participants also had a relative high VVV. Another limitation of our analyses is that they are based on a randomized controlled trial population. The intervention may have influenced variability, particularly early on in the study when hypertension was newly diagnosed. However, in our stratified analysis the influence of randomization group appeared minimal and the difference in BP reduction between intervention and control groups was small. We did not collect data on dosage of antihypertensive medication and time of day of the BP measurement. We could therefore not assess the influence of these factors on VVV. We were, however, able to assess the influence of adherence to antihypertensive treatment and seasonal change. Stroke occurrence is possibly underreported in our study due to the fact that it was not collected separately from TIA during the early phases of the study, and incident cases in the first four years of follow-up were therefore not included in the analyses. However, these events were missing for all participants and it is unlikely that this influenced the association with VVV.

In conclusion, in our study population of community-dwelling older people VVV is not associated with an increased risk of dementia over six years of follow-up. Future research is needed to confirm the findings of this study and assess whether other associations between VVV and incident dementia might exist including at a younger age and if followed over longer periods. We found a significant association with decline in MMSE, but its clinical relevance is uncertain. High VVV was associated with more incident CVD.

SUPPLEMENTARY MATERIAL

Supplement appendix 1. Statistical analysis

We used the Statistical Package for Social Sciences version 23.0 (SPSS Inc., Chicago IL, USA) for the Cox proportional hazards regression. R studio version 3.2 was used for the general linear mixed-effects model, with R-package 'LME4', and for the competing risk analysis, with R-package 'survival'.[42,88,89] For the general linear mixed-effects model we used MMSE as continuous variable. However, because the MMSE data were not normally distributed, we repeated our analyses with an individually calculated value of decrease in MMSE from baseline. This gave comparable results. We presented our results on the raw MMSE scores as these were more easy to interpret.

Missing data

	Variables	Participants with missing data (number, %)
Main analyses	Visit-to-visit variability	0 (0.0%)
	Dementia	30 (1.3%)
	Cognitive decline	0 (0.0%)
	Cardiovascular disease	0 (0.0%)
Confounding variables	Gender	0 (0.0%)
	Age	0 (0.0%)
	Education	19 (0.8%)
	BMI	1 (0.0%)
	LDL cholesterol	48 (2.1%)
	Smoking	6 (0.3%)
	Diabetes mellitus	0 (0.0%)
Sensitivity analyses	Mortality	4 (0.2%)
	Randomisation group	0 (0.0%)
	Antihypertensive medication	2 (0.1%)
	Medical adherence	650 (28.2%)
	Seasonal change	0 (0.0%)

Number of participants with missing data for each variable of interest. Percentage calculated is based on all participants included in the analyses (n=2305). BMI indicates body-mass index; LDL, low-density lipoprotein.

Supplement Table 1 - Baseline characteristics of participants included or excluded from analyses

	Participants included in analyses (n=2305)	Participants excluded from analyses (n=1221)	P value
Gender (male)	1032 (44.8%)	575 (47.1%)	0.19
Age	74.2 (2.5)	74.7 (2.5)	<0.01
Low educational level	493 (21.6%)	343 (28.5%)	<0.01
History of CVD	756 (33.0%)	473 (39.0%)	<0.01
DM	437 (19.0%)	209 (17.1%)	0.18
Hypertension*	2049 (88.9%)	1101 (90.3%)	0.21
Antihypertensive medication	1246 (54.1%)	705 (57.9%)	0.03
Systolic BP	154.7 (20.8)	156.5 (22.3)	0.02
Diastolic BP	81.3 (10.6)	81.7 (11.8)	0.36
BMI	27.5 (4.2)	27.4 (4.1)	0.69
LDL cholesterol	3.1 (1.0)	3.1 (1.0)	0.45
Current smoker (yes)	279 (12.1%)	189 (15.5%)	0.01
MMSE	28.3 (1.6)	27.8 (1.9)	<0.01
Randomisation (intervention)	1233 (53.5%)	657 (53.8%)	0.86

*Data are presented as frequency (%) or mean (SD). *Hypertension was defined as a systolic blood pressure at baseline ≥140 mmHg, a diastolic blood pressure at baseline ≥90 mmHg or the use of antihypertensive medication. CVD indicates cardiovascular disease; DM, diabetes mellitus; BP, blood pressure; BMI, body mass index; LDL, low-density lipoprotein; MMSE, mini-mental state examination.*

Supplement Table 2 - Predefined visit-to-visit variability measures and their association with dementia

		Mean (SD)	Hazard ratio (95% CI)	P value
SBP	**CV**	9.0 (4.5)	1.00 (0.96-1.05)	0.85
	SD	13.6 (6.9)	1.00 (0.97-1.03)	0.97
	VIM	2.3 (1.1)	1.02 (0.86-1.21)	0.82
	ARV	6.2 (20.6)	1.01 (1.00-1.02)	0.04
	Delta	30.7 (15.9)	0.99 (0.98-1.00)	0.18
DBP	**CV**	9.0 (4.4)	1.01 (0.97-1.06)	0.54
	SD	7.1 (3.5)	1.02 (0.97-1.08)	0.46
	VIM	2.8 (1.4)	1.05 (0.91-1.20)	0.53
	ARV	3.8 (10.3)	1.00 (0.98-1.02)	0.88
	Delta	16.0 (8.2)	0.99 (0.97-1.02)	0.44

Analyses are fully adjusted (model 3). The hazard ratio is per one point increase in CV/SD/VIM/ARV/delta. SD indicates standard deviation; CI, confidence interval; SBP, systolic blood pressure; CV, coefficient of variation; VIM, variation independent of mean; ARV, average real variability; DBP, diastolic blood pressure. A P value of <0.006 was considered statistically significant after Bonferroni correction.

Supplement Table 3 - Number of patients with dementia in each predefined category

	Dementia cases	(%)	HR	(95% CI)
Stable normotension	11 / 181	(6.1%)	Ref.	
Episodic moderate hypertension	58 / 1109	(5.2%)	0.76	(0.40-1.45)
Episodic severe hypertension	8 / 199	(4.0%)	0.57	(0.23-1.41)
Stable hypertension	33 / 786	(4.2%)	0.64	(0.32-1.27)

The mutually exclusive categories are based on the minimum and maximum systolic blood pressure. Stable normotension is defined as a maximum systolic blood pressure ≤140 mmHg; episodic moderate hypertension as a minimum systolic blood pressure ≤140 mmHg and maximum 140-179 mmHg; episodic severe hypertension as a minimum systolic blood pressure ≤140 mmHg and maximum ≥180 mmHg; and stable hypertension as a minimum systolic blood pressure >140 mmHg. Analyses are unadjusted due to the small number of dementia cases in some groups.

Supplement Table 4 - Result of the association between visit-to-visit variability and MMSE during follow-up

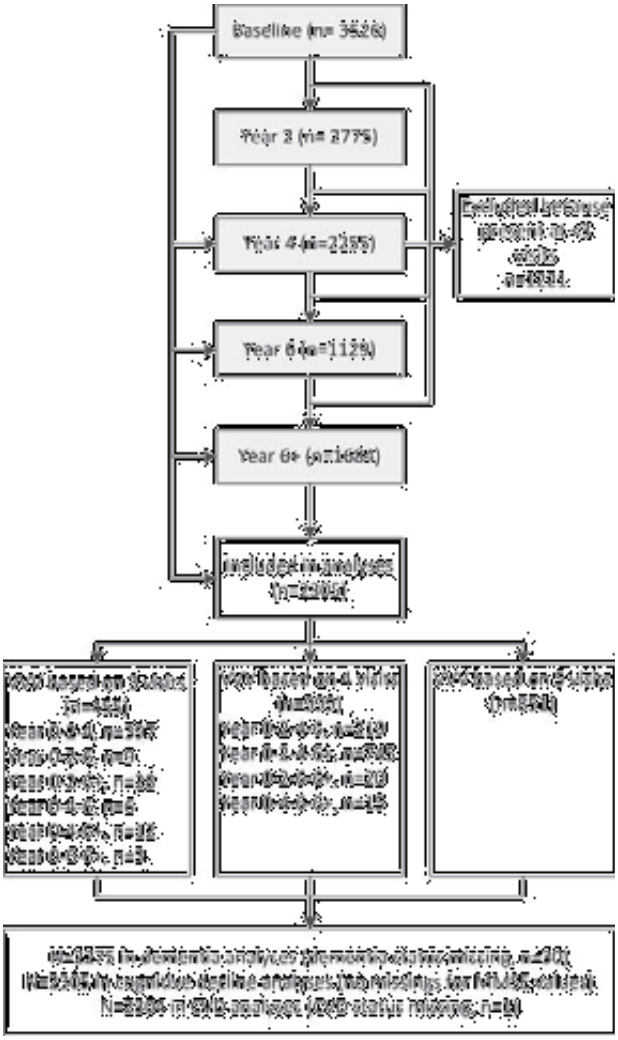
	Beta	(95% CI)
Intercept (VVV Q1)	28.42	(28.29 to 28.55)
VVV Q2	-0.12	(-0.30 to 0.06)
VVV Q3	-0.05	(-0.23 to 0.13)
VVV Q4	-0.18	(-0.36 to 0.00)
Visit (VVV Q1 × Visit)	0.03	(-0.03 to 0.08)
VVV Q2 × Visit	0.02	(-0.06 to 0.10)
VVV Q3 × Visit	-0.05	(-0.12 to 0.03)
VVV Q4 × Visit	-0.09	(-0.17 to -0.01)

*Visit-to-visit variability (VVV) is divided into quartiles. Quartile 1 includes CV of SBP 0.4 to 5.9; quartile 2, CV of SBP 5.9 to 8.4; quartile 3, CV of SBP 8.4 to 11.3; quartile 4, CV of SBP 11.3 to 36.0. The intercept indicates the mean MMSE at baseline for quartile 1. VVV indicates the mean difference in MMSE per quartile at baseline. Visit indicates mean change in MMSE in quartile 1 per visit. The interaction term (Q2/3/4 * Visit) determines whether the VVV quartiles experience significant difference in longitudinal changes over time. Analyses are adjusted for gender, age, low educational level, obesity, low-density-lipoprotein, smoking and diabetes. CI indicates confidence interval; VVV, visit-to-visit variability; Q, quartile.*

Supplement Table 5 - Competing risk analysis

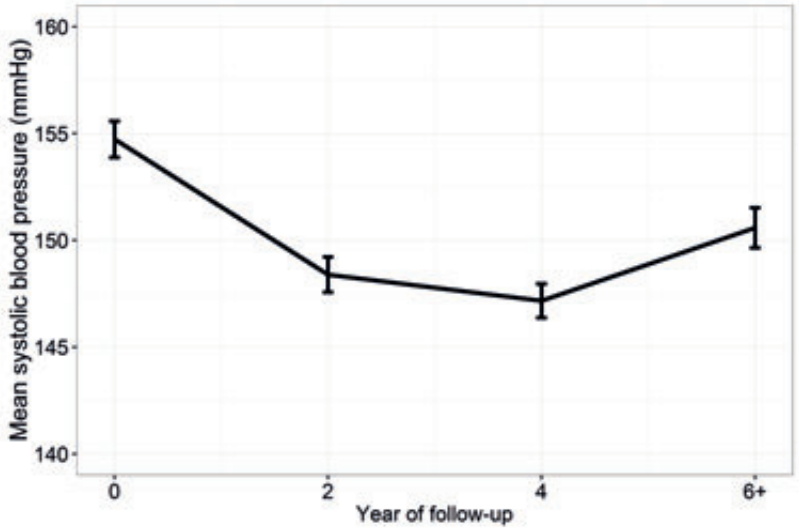
	Survival CSHR (95% CI)	Mortality CSHR (95% CI)	Dementia CSHR (95% CI)	Dementia SHR (95% CI)
Model 1	0.99 (0.98-1.01)	1.01 (0.97-1.04)	1.00 (0.96-1.05)	1.00 (0.96-1.05)
Model 2	1.00 (0.99-1.01)	1.01 (0.97-1.04)	1.00 (0.96-1.05)	1.01 (0.96-1.05)
Model 3	1.00 (0.99-1.01)	1.00 (0.96-1.04)	1.00 (0.96-1.05)	1.01 (0.96-1.05)

A competing risk analysis for the association between visit-to-visit variability and dementia, while accounting for the competing event of mortality. The cause specific hazard ratio (CSHR) estimates the direct effect of blood pressure variability on the various outcomes (i.e., survival, mortality and dementia). The subdistribution hazard ratio (SHR) describes the risk of dementia while accounting for the competing event mortality.



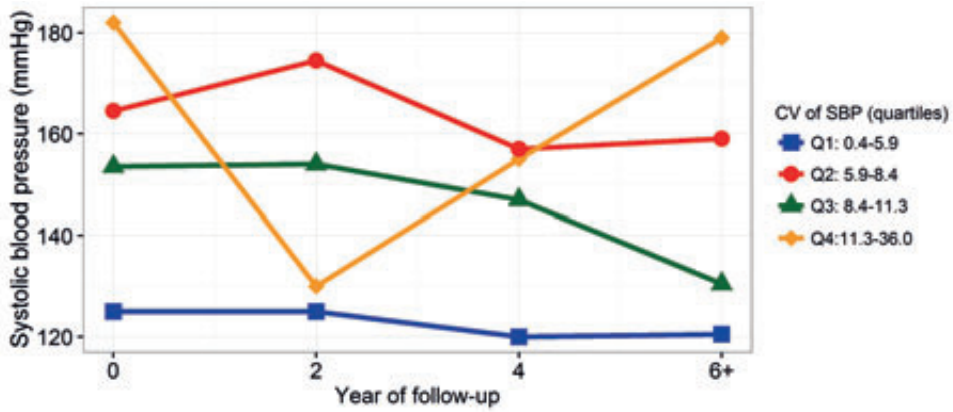
Supplement Figure 1 - Flow-diagram of the number of participants in- and excluded from the analyses

The grey boxes indicate the number of participants at each follow-up visit of the complete preDIVA study population. The white boxes indicate the number of participant included and excluded in our analyses. Participants were included in the analyses if they had a valid blood pressure measurement at ≥3 visits. Participants with different intervals in between the blood pressure measurements were included. N indicates the number of participants; VVV, visit-to-visit variability; MMSE, mini-mental state examination; CVD, cardiovascular disease.



Supplement Figure 2 - Mean (95% confidence interval) systolic blood pressure during follow-up

Mean systolic blood pressure of all participants included in the analyses. Year 6+ includes the systolic blood pressure of participants with a visit at eigth or six years follow-up. N indicates the number of participant at each visit.



Supplement Figure 3 - Examples of the course in systolic blood pressure during follow-up per quartile of visit-to-visit variability

Visit-to-visit variability quartiles are based on the coefficient of variation (CV) of systolic blood pressure (SBP). Quartile 1 (Q1) includes participants with a CV of SBP of 0.4-5.9, the illustrated participant has a CV of SBP of 2.4. Quartile 2 (Q2) includes participants with a CV of SBP of 5.9-8.4, the illustrated participant has a CV of SBP of 6.6. Quartile 3 (Q3) includes participants with a CV of SBP of 8.4-11.3, the illustrated participant has a CV of SBP of 8.54. Quartile 4 (Q4) includes participants with a CV of SBP of 11.3-36.0, the illustrated participant has a CV of SBP of 14.7. Year 6+ includes the systolic blood pressure of participants with a visit at eigth or six years follow-up. CV indicates coefficient of variation; SBP, systolic blood pressure; Q, quartile.

PRESCRIBING AND DEPRESCRIBING ANTIHYPERTENSIVE MEDICATION IN OLDER PEOPLE BY DUTCH GENERAL PRACTITIONERS

A QUALITATIVE STUDY

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ABSTRACT

Objectives To explore general practitioners' (GPs) routines and considerations on (de) prescribing antihypertensive medication (AHM) in older patients, their judgement on usability of the current guideline and needs for future support.

Design Semistructured interviews.

Setting Dutch general practice.

Participants Fifteen GPs were purposively sampled based on level of experience and practice characteristics until saturation was reached.

Results GPs appeared reluctant to start AHM, especially in patient >80 years. High systolic blood pressure and history of cardiovascular disease or diabetes were enablers to start or intensify treatment. Reasons to refrain from this were frailty and patient preference. GPs described a tendency to continue AHM regimens unchanged, influenced by daily time constraints, automated prescription routines and anticipating discomfort when disturbing patients' delicate balance. GPs were only inclined to deprescribe AHM in terminally ill patients or after prolonged achievement of target levels in combination with side effects or patient preference. Deprescription was facilitated when GPs had experience with patients showing increased quality of life after deprescription and was withheld by anticipated regret (ie, GPs' fear of a stroke after deprescribing). GPs felt insufficient guidance from current guidelines, especially on deprescription.

Conclusions GPs are reluctant to start or deprescribe AHM in older people and have a propensity to continue AHM within a daily routine that insufficiently supports critical medication review. (De)prescription is influenced by patient preferences and anticipated regret and current guidelines provide insufficient guidance.

INTRODUCTION

Eighty percent of older people with hypertension use antihypertensive medication (AHM).[90] However, treatment recommendations for people aged 65 and over are limited and there is considerable variation in treatment policy between general practitioners (GPs).[31,91] The European guideline on cardiovascular disease (CVD) prevention states that in this older population AHM is still effective, but that for people over 80 years old target systolic blood pressure (SBP) levels may be less strict (eg, 140-150 mmHg instead of <140 mmHg).[31] No recommendations are provided on deprescription (ie, decreasing dosage or discontinuing). In the past, older people were mostly excluded from clinical trials on AHM and cardiovascular prevention. More recent studies that have included this group have presented conflicting results. Overall, antihypertensive treatment in the oldest old (>80 years) seems to reduce cardiovascular morbidity but has no effect on overall mortality.[92] The *Systolic Blood Pressure Intervention Trial* (SPRINT) provided evidence that intensive blood pressure (BP) control to a target SBP of below 120 mmHg could prevent CVD and mortality, also in people aged ≥75 years.[93,94] This trial also showed that a low target SBP did not result in more orthostatic hypotension, falls or acute kidney injury, which are concerns regarding intensive BP treatment.[95] However, it remains unclear to what extent these results are generalizable.[96,97] On the other end of the spectrum, observational studies have shown that in frail people >80 years old a BP below 140/90 mmHg might even be harmful as it is associated with an increased mortality risk.[98] In these oldest old people it may therefore be recommended to restrict to two antihypertensive drugs and aim for a maximum reduction in SBP of 15 mmHg.[92,98] This is, however, not included in the current guidelines.

Our primary aim was to explore GPs' routines and considerations on prescribing and deprescribing AHM in older people to clarify the processes underlying current (de) prescribing practices. Our secondary aim was to assess GPs' judgement on usability of current guideline and their needs for future support in this decision-making process to help improve future guidelines on antihypertensive treatment in older people.

METHODS

Participants

Between October 2015 and December 2016, 15 semi-structured interviews were performed. The study was granted a waiver from ethical approval by the Medical Ethics Committee of the Academic Medical Center (AMC) in Amsterdam. All participants gave written informed consent. GPs from different geographical areas in the Netherlands were invited by telephone or e-mail to participate in the interviews. Participants were purposively sampled based on years of experience, setting (rural or urban) and type of practice (small-scale vs

healthcare centre), presence of a practice nurse and expertise with regard to cardiovascular risk management. Of the 44 GPs approached, 15 agreed to participate, 13 could not be reached and 16 refused participation. Main reason GPs declined to participate was time constraint. After 15 interviews, saturation was reached as no important new (sub)themes emerged over the last interviews.

Data collection

Each interview was done by one of two researchers (TvM and SI), both young female physicians trained in qualitative interviewing. The interviewers and interviewees had no prior relationship and they were aware of each other's profession and level of experience. A prepiloted semistructured interview guide (box 1) was developed focused on behaviour and attitude in daily clinical practice to make the interview as concrete as possible and limit the influence of socially desirable answers.[99] First, participating GPs were asked to retrieve recent case histories on antihypertensive treatment in older patients. They were primed for cases in which they recently started, increased, continued (without changes), decreased or discontinued AHM and were asked to elaborate on their routines and considerations in the treatment decision. It was left to the discretion of the GPs to decide who they considered an older patient. They were allowed to consult their electronic health record for further details. Second, their views on the value of the current guideline and needs for future support were discussed. The interviews were held in person, at a place that was convenient for the interviewed GP (at their practice or home or at the AMC or Radboud University Medical Center). The interviews took approximately 45 minutes, were audio-recorded and transcribed by the interviewer verbatim.

Box 1 - Main topics in the interview guide

- Start or increase AHM: patient from daily practice
- Continue AHM: patient from daily practice
- Deprescribe AHM: patient from daily practice
- Current guideline
- Needs and wishes for future guideline support

AHM indicates antihypertensive medication.

Data analysis

Transcripts were thematically analysed following an inductive and iterative approach.[100] Two researchers (TvM and SI) independently coded all transcripts. After every two to four interviews, the researchers discussed the codes and through comparison and discussion a common coding system was developed. The (sub)themes derived from the codes were

subsequently organized within the prespecified structure on AHM (de)prescription: starting, intensifying, continuing and deprescribing. At multiple times during the data collection and analysis phase, results were discussed among a team including a practising GP and an expert in qualitative research. Based on these discussions, the interview guide was adapted by adding reflective questions to study the contrast between routine behaviour and conscious considerations. Also, the tilting point for (de)prescription was further specified and the reasons for starting AHM were further explored as this is under-represented at the start.

Patient and Public Involvement

By exploring GPs' routines and views, we aim to describe daily clinical practice and the support necessary to improve clinical practice from a GP's perspective.

RESULTS

Fifteen GPs were interviewed varying in years of experience from 1 to 30 years (Table 1). In daily practice, (de)prescription of AHM was consciously evaluated when practice nurses noticed a high BP in patients with a history of CVD, or when patients actively approached their GP for their BP, had their BP measured for other reasons, for example when moving to an elderly home, or underwent a critical review on polypharmacy in collaboration with the pharmacist. In table 2, the main barriers and enablers that GPs mentioned when starting, intensifying, continuing and deprescribing AHM are presented, illustrated by four cases (Table 3). These barriers and enablers are further explained in the text below.

Starting treatment

In general, GPs were somewhat reluctant to start AHM in older patients. This was especially true for the oldest old patients (>80 years), for patients with a limited life expectancy (<1-2 year) and for frail patients. In these cases, GPs only started AHM when SBP was higher than 180 mmHg. GPs evaluated frailty based on their clinical impression and physical, cognitive and overall functioning. One GP was cautious because of the psychological impact starting medication could have on patients:

> *"Sometimes I think that the added value (of starting AHM) in patients at older ages is minimal, but it does have a huge impact if I say, 'Well you have a high BP and you need medication for it'. I think in some cases I am inclined to say to myself, 'Well then just leave it' [don't start AHM]." [GP 3, male, 5-10 years' experience as GP]*

GPs felt more inclined to start AHM in patients with a history of CVD (ie, secondary prevention) or diabetes and in case of a planned operation. GPs were reluctant to start

Table 1 - Participant characteristics

Characteristic		Population (n=15)
Sex (male)		8 (53%)
Age	<40 years	7 (47%)
	40-50 years	3 (20%)
	>50 years	5 (33%)
Years as a GP	0-5 years	4 (27%)
	5-10 years	3 (20%)
	10-15 years	3 (20%)
	>15 years	5 (33%)
Academically affiliated*		7 (47%)
Location	Urban	8 (53%)
	Rural	7 (47%)
Practice type	Solo	2 (13%)
	Duo	4 (27%)
	Group	8 (53%)
	Other**	1 (7%)
Practice nurse available		10 (67%)

*Characteristics of the participating general practitioners. *Academically affiliated indicates either working at an academic centre for educational or research purpose or working as GP trainer. **One GP worked as locum GP in different practices. GP indicates general practitioner; M, male; F, female.*

Table 2 - Main barriers and enablers to start, intensify, continue or deprescribe antihypertensive medication

	Enabler	Barrier
Starting AHM	High SBP (>180 mmHg) History of CVD/DM Planned operation Patient preference	Age >80 years Limited life expectancy Frailty Psychological impact of starting medication Patient preference
Intensifying AHM	High SBP (>140 or >160 mmHg) Age <80 years History of CVD/DM	Age >80 years ≥3 antihypertensive drugs Patient preference Frailty
Continuing AHM	Automated prescription routines Time constraints Requires less justification than deprescribing/intensifying Anticipating discomfort when disturbing the precarious balance Target BP level not yet reached	
Deprescribing AHM	Prolonged achievement of target BP Side effects, orthostatic hypotension Risk of falling Patient preference Experience with increase in quality of life Terminal illness	Anticipated regret Deprescribing may give the impression of giving up on a patient AHM gives patients a sense of control

AHM indicates antihypertensive medication; CVD, cardiovascular disease; DM, diabetes mellitus; SBP, systolic blood pressure; BP, blood pressure.

AHM when patients felt resistant towards medication or, on the contrary, were inclined to start AHM when patients were fearful for the consequences of a high BP:

"I have an older female who was very afraid for her high BP. She used to have an angiotensin-converting enzyme (ACE) inhibitor which I stopped, or reduced. I strictly monitored her BP for 6 months; during which it was always good. And then, a few months later, it went up again; systolic [BP] around 190 or 200. And then she became very anxious. So she wanted her ACE-inhibitor back." [GP 1, male, >15 years' experience]

Table 3 - Quotes about patient cases to illustrate antihypertensive medication (de)prescription

Start AHM	*"We had a woman who just moved into an elderly home and came under our care. This is a woman of 91 years old. She came to live there with her husband, because of her age and because she had mild dementia. And when she arrived at the home for elderly they immediately measured her BP. She had a BP of 190 over 90. And so we gave her losartan 50 mg. […] So before that she had no AHM. Well you may think, that doesn't do much, it isn't that much. And so, we gave it. Then her BP immediately went to 140 over 80 and it remained there. And then she started complaining about terrible dizziness. And so I stopped it again." [GP 12, female, >15 years' experience as GP]*
Intensify AHM	*"This is also a very fit lady, but she is 86 years old. She had hydrochlorothiaizde 12.5 mg and we increased that to 25 mg, because she had a BP of 180 over 80. And now with 25 mg it is 160 over 80. And she feels fine, so we leave it like this." [GP 6, female, 10-15 years' experience]*
Continue AHM	*"A patient of 92 years old, I think. Known with heart failure, poor mobility and COPD. She wants as little as possible. Also she doesn't want to go to the hospital. And her BP is actually not much of an issue. Even though we know it is higher from time to time. When the edema increases, her legs are swollen and she gets shortness of breath on exertion, well then we always measure the BP to see how much room we have to increase the furosemide. And there is always enough room, she always has a BP of 170-180. So that is nice, that we have that. But it never crossed my mind, when we have treated the fluid retention, to follow-up on her BP to say, let's see if we should treat this structurally." [GP 15, female, 10-15 years' experience]*
De-prescribe AHM	*"Here I have the file of a 69 years old woman who has stage 4 lung cancer with progressive brain metastases. […] Because of a language barrier, her daughter explained that her mother often felt dizzy when getting up. She first called it vertigo, but after some further questioning it appeared more like light headedness. […] Her BP was repeatedly around 124 over 70. And what I did was, first I stopped the hydrochlorothiazide. Then her BP stayed low and she was still dizzy. And in the end I also stopped her losartan. […] And now her BP stays around 130 over 80, but now without any AHM. So in hindsight I think she was severely over-treated." [GP 11, male, 0-5 years' experience]*

AHM indicates antihypertensive medication; BP, blood pressure; GP, general practitioner; COPD, chronic obstructive pulmonary disease.

Intensifying treatment

Intensifying treatment in patients already receiving AHM (ie, increasing dosage and/or supplementing by adding another antihypertensive drug) seemed relatively straightforward. This was proposed for a SBP higher than 140 mmHg in patients younger than 80 years or with a history of CVD or diabetes and for SBP readings higher than 160 mmHg in patients older than 80 years. GPs experienced more uncertainty when patients already used at least three antihypertensive drugs or when patients wished to refrain from intensifying treatment:

"I often see that people do not want this much medication. That they just want to feel comfortable at home. Then (at older ages) you will look more at the person behind the illness." [GP 5, male, >15 years' experience]

Another reason not intensify treatment was frailty:

(Interviewer: How does frailty influence your choice with regard to AHM?) "That your target BP is less strict. That you will accept a BP of 165 over 95 and not give someone extra medication. While in the fit older patient you will think, let's give it a go (increase AHM)." [GP 2, female, 10-15 years' experience]

Continuation of treatment

Continuation of AHM with unchanged regimens was often not an active choice but a consequence of automated repeat prescription algorithms in the electronic health record. In combination with time constraints within the general practice organisation, this prompted swift, global checks of AHM regimens only without room for an assessment whether the prescribed medication was still appropriate. In some cases, GPs thought it might have been better if they deprescribed AHM; however, they felt that leaving the drug regimen unaltered would require less justification than changing things around:

"I also think that it is easier to simply continue a treatment. I feel that changing a treatment requires much more justification and should also be done in consultation with the patient or family. Sometimes it can be easier to just consent to a repeat prescription, than to repeatedly consider whether it is still appropriate." [GP 8, male, 0-15 years' experience]

When continuation of AHM was an active choice, an important motivation for leaving things as they were was the perception that some patients had found a precarious balance and changing AHM (ie, increasing or decreasing) could increase the risk of discomfort:

"And reducing, well I think that… it's like 'never change a winning team'. If someone is doing well and has no complaints, then you are not inclined to...(change AHM)." [GP12, female, >15 years' experience]

Finally, one GP thought that aiming for a certain BP target also contributed to the steady state in repeat AHM prescriptions, which kept her from regularly re-evaluating whether they were still appropriate:

"I think that, if I look at my experience, when you have made the decision to act on a BP, I think that you are more inclined to continue your aim for the target BP that you have set. […] I think that you tend to just proceed and not use every evaluation moment to reconsider whether you should continue with it [treatment]. Which really would have been very appropriate. But I notice that I do not do that myself." [GP 15, female, 5-10 years' experience]

Deprescribing treatment

Reducing or discontinuing AHM was not something that was easily decided on. It required clear motives apart from a prolonged period during which the BP was at or below target level, including side effects of AHM, orthostatic hypotension, a high risk of falling and patient preference. Some GPs had experience with an increase in quality of life (for example feeling less tired) of patients after deprescribing AHM:

> *"When I stop AHM in older patients they often feel much better. Then the BP rises somewhat and they feel less tired. Well I don't know if it is caused by that, but sometimes I think that." [GP 1, male, >15 years' experience]*

In some cases, the decision of GPs was influenced by anticipated regret: the fear that a patient might have a stroke after deprescribing AHM:

> *"And it requires a sort of courage to notice that when you reduce AHM, the values, the indicators, increase. And you have to feel comfortable with that. If you withdraw AHM and someone, say after six months, has a stroke, than you suddenly feel uncomfortable." [GP 5, male, >15 years' experience]*

GPs acknowledged that in the terminal phase it would be rational to discontinue AHM. However, they often hesitated to take this step, to avoid the impression they were giving up on the patient or unnecessarily deprive them of a sense of being in control with adequate BP measurements. They aimed to avert the risk of non-fatal stroke and the accompanying functional limitations in the last phase of life.

Current guideline and future support

The interviewed GPs often came to new insights and ideas during the interview, when provided with ample time to reflect on decisions that they had made. They stated that in daily practice treatment decisions were often based on intuition and that it might have been better if they had deprescribed AHM earlier:

> *"I often do this briefly in between my consultations. And I notice, now that we are talking about it… it forces you to critically think about it. And then I think, oh I could do this better. And of course we can always do our work better; nobody knows everything. But I do think that, now that you mention this and we critically look at it, I should think this through more thoroughly." [GP 11, male, 0-5 years' experience]*

GPs generally felt insufficiently supported by the guidelines in their efforts to treat hypertension in older people:

> *"Yes, whom to treat and whom not to treat among the oldest old. […] The healthy you have to treat, because they still have a long life expectancy and therefore have much to gain in lowering their BP. Those with diseases, like the patients with diabetes or a myocardial infarction, you have to treat because they have a substantially elevated risk because of*

their disease that we are well able to bring down. That group in between, with frail elderly, I followed the advice not to treat them for a while. And now I recently heard that you also have to treat those. I just don't know it anymore. I would really like to have a guideline that states: in elderly you have pay attention to this, this and this." [GP 9, female, 5-10 years' experience]

A GP suggested a treatment flow diagram including more subjective factors like frailty for future support or indicators to start or deprescribe AHM like the Screening Tool of Older Person's Prescriptions (STOPP)/Screening Tool to Alert doctors to Right Treatment (START) criteria.[101] Another suggestion was to aid deprescription by incorporating algorithms in the electronic health record that aid doctors and practice nurses in observing complaints that are potentially related to a low BP.

DISCUSSION

For Dutch GPs, starting or intensifying antihypertensive medication is guided by the absolute level of SBP, history of CVD and diabetes. GPs feel reluctant to start AHM at older age, but when someone already receives AHM they also feel reticent in accepting a high BP (ie, not intensifying AHM). They may refrain from intensifying AHM in cases of frailty or clear patient preference. There is a propensity to continue AHM in older people within a daily routine that insufficiently supports critical review of prescriptions due to time constraints and automated prescription routines. Continuation of AHM is also supported by anticipating discomfort when disturbing patients' delicate balance and the perception that continuing treatment requires less justification. The decision to deprescribe AHM is difficult, although GPs also mention a possible gain in quality of life, such as less fatigue. Deprescription is only considered when BP is consistently at or below the target and a patient experiences side effects or wants to reduce treatment. Anticipated regret of a future stroke may represent an additional barrier for deprescription. GPs experience insufficient guidance on antihypertensive treatment for older people and would welcome a treatment flow diagram including specific STOPP criteria as well as more subjective factors like frailty.

An important strength of our study is the diversity of GPs that were interviewed, with a broad range in experience and setting. The interview guide was aimed at discussing examples from daily clinical practice to limit the chance of socially desirable answers. We followed the consolidated criteria for reporting qualitative research (COREQ) guidelines to improve the interpretation and reproducibility of our results.[102] A limitation is that our study only includes Dutch GPs, which may restrict the level of generalisability. The role of Dutch practice nurses within the cardiovascular prevention programmes has become more prominent over the last years (box 2).[103] This probably limits the time Dutch GPs spend on antihypertensive treatment and may facilitate routine continuation of AHM. Since specific directives on BP treatment for older people are lacking in most international guidelines, the

feeling of limited support is likely found in other countries as well. Relative few patient cases were discussed were AHM was started, due to the reluctance of GPs to start AHM in older patients and the notion that a lot of the older patients already received AHM. Even though data saturation was reached, this could have potentially limited the scope of reasons to start AHM.

Box 2 - Antihypertensive treatment in Dutch general practices

- Almost all Dutch citizens are registered at a general practice.
- In the Netherlands, general practitioners (GPs) have a gatekeeping role and are relatively easy accessible.[104]
- Approximately 75-80% of medication is therefore prescribed by GPs.[105]
- In 2006, the guideline on hypertensive treatment was combined into a more general guideline on cardiovascular risk management (CVRM).[106]
- Recommendations in this guideline are similar to the European guideline, aside from the Systematic Coronary Risk Estimation chart which is expanded up to 70 years and the target systolic blood pressure for people over 80 years old which is 150-160 mmHg.[31]
- With the introduction of nurse-led CVRM, over the last decade, the workload for GPs decreased and guideline adherence improved.[107]
- Specialists are mainly responsible for starting antihypertensive treatment in patients with secondary prevention, while general practitioners play a crucial part in primary prevention.

No other qualitative study has assessed GPs' reasons for prescription and deprescription of antihypertensive medication in older patients. There are however previously reported studies with a broader focus on cardiovascular prevention, which have shown results consistent to ours.[108-110] These studies stated that GPs are uncertain about many aspects of cardiovascular prevention, including the application of guidelines, organisation of care and benefit for individual patients and that they are less likely to prescribe preventive medication in frail older people.[91,108,109] Especially when focusing on AHM, the uncertainties are most likely fuelled by the conflicting available evidence. There is both evidence in favour of intensifying treatment as well as studies that support a higher target BP.[94,98] These uncertainties may lead to overtreatment, by unnecessary continuation of AHM regimens, or to undertreatment, caused by the reluctance to initiate treatment in older people who are still free from AHM. As continuation also seems to be a consequence of daily routine influenced by time constraints and automated prescription routines, overtreatment might be prevented by more structural time for medication reviews. Patient preference plays a crucial part in (de)prescribing and should be actively taken into consideration, for example through use of the outcome prioritization tool.[111] In addition, an estimation of frailty seems important which, by its subjective nature, could bring about the large variation in treatment intentions of GPs, which was previously described in a Belgian vignette study.[112]
The reluctance to deprescribe AHM in older patient, is also noted for other drug classes.[113] This reluctance is, among other factors, induced by GPs' anticipated regret, which has been

previously described as a motivator to start or continue preventive treatment.[109,114] The fear of 'causing' a stroke by deprescribing AHM is unsupported by clinical evidence but might be instigated by results from trials like the SPRINT trial that support intensive BP lowering,[94] even though multimorbid older people are potentially under-represented in this trial and the generalisability of these results is uncertain.[96] Also for deprescribing shared decision-making is crucial.[113] Older patients have varied attitudes and ideas about their medication use and clear communication is therefore crucial.[115] However, given the present knowledge gaps, risk communication is perceived difficult by GPs.[116] Until now, deprescribing AHM is only supported by observational studies, which have demonstrated an association between a low or decreasing BP and worse functional outcome, cognitive decline and increased mortality.[117,118] The *Discontinuation of Antihypertensive Treatment in Elderly People* (DANTE) trial showed that discontinuation of AHM was safe, albeit not beneficial on cognitive, psychological or general daily functioning during the relative short 16-week follow-up.[24] To make a better informed decision on the deprescription of AHM, it would be useful to have additional evidence on the efficacy of deprescription with longer follow-up and on the subjective and objective impact of AHM in older people. For GPs, it would be desirable to add indicators for deprescription (ie, STOPP criteria) in the guideline as this is what GPs consider difficult.

Dutch GPs are reluctant to start or deprescribe AHM in older people. Continuation of AHM is reinforced by a daily routine that insufficiently supports critical medication review and conflicting available evidence on efficacy of intensifying treatment. Patient preference appears crucial for both prescribing and deprescribing. Anticipated regret of a future stroke works as a barrier for deprescription. Current guidelines provide insufficient guidance and clear indicators on deprescription could endorse it.

MODIFIABLE DEMENTIA RISK SCORE TO STUDY HETEROGENEITY IN TREATMENT EFFECT OF A DEMENTIA PREVENTION TRIAL

A POST HOC ANALYSIS IN THE PREDIVA TRIAL USING THE LIBRA INDEX

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ABSTRACT

Background Selecting high-risk participants for dementia prevention trials based on a modifiable dementia risk score may be advantageous, as it increases the opportunity for intervention. We studied whether a multi-domain intervention can prevent all-cause dementia and cognitive decline in older people across three different levels of a modifiable dementia risk score.

Methods *Prevention of Dementia by Intensive Vascular Care* (preDIVA) is a randomised controlled trial studying the effect of multi-domain vascular care during 6-8 years on incident all-cause dementia in community-dwelling people aged 70-78 years. For this post hoc analysis, we stratified preDIVA participants in tertiles based on their baseline *LIfestyle for BRAin health* (LIBRA) index, a modifiable dementia risk score. With Cox proportional hazards regression, the intervention effect on dementia was assessed. The effect on cognition was measured every two years with the Mini-Mental State Examination and Visual Association Test.

Results Dementia developed in 220 of 3274 (6.7%) participants. In participants with a low, intermediate and high LIBRA index, the hazard ratio (HR) of the intervention on incident dementia was respectively 0.71 (95% CI 0.45-1.12), 1.06 (95% CI 0.66-1.69) and 1.02 (95% CI 0.64-1.62). Also, when adding the non-modifiable risk factors age, education and sex to the index, results were comparable (respectively; HR 0.88, 95% CI 0.54-1.43; HR 0.91, 95% CI 0.57-1.47; HR 0.92, 95% CI 0.59-1.41). There was no statistically significant intervention effect on cognition during follow-up across the LIBRA groups.

Conclusions In the preDIVA study population aged 70-78 years, the LIBRA modifiable dementia risk score did not identify a (high) risk group in whom the multi-domain intervention was effective in preventing dementia or cognitive decline.

Trial registration ISRCTN, ISRCTN29711771. Registered February 14th 2006, http://www.isrctn.com/ISRCTN29711771.

BACKGROUND

The number of dementia cases worldwide is anticipated to double over the coming two decades.[2,119] Up to a third of Alzheimer's disease cases may be attributable to potentially modifiable risk factors, including several vascular risk factors such as diabetes mellitus, midlife hypertension and physical inactivity.[10] This offers a window of opportunity for prevention strategies. However, selection of the optimal target population when designing a randomised controlled trial (RCT) to prevent dementia remains a challenge.[28] Results from recent RCTs suggest that interventions may be most effective in those at increased risk of dementia based on the presence of one or more dementia risk factors.[14-16] In such an at risk population the potential to improve modifiable risk factors, such as hypertension and physical inactivity, and thereby prevent dementia, is higher. In addition, the higher dementia incidence rates in high risk populations increase the study power, decreasing the total number of participants required to demonstrate a treatment effect.

A dementia risk score could be a useful tool to recruit a high-risk population for prevention trials. Most risk scores that have been developed are, however, heavily dependent on non-modifiable risk factors such as age, sex and education.[120] The *LIfestyle for BRAin health* (LIBRA) index is the first, and so far only, validated dementia risk score predominantly supported by modifiable health and lifestyle factors.[121] It consists of the following 12 risk and protective factors: depression, hypertension, obesity, smoking, hypercholesterolemia, diabetes, renal dysfunction, physical inactivity, coronary heart disease, low/moderate alcohol use, cognitive activity and adherence to the Mediterranean diet. As it reflects an individual's potential for dementia prevention, it may identify those most responsive to an intervention.

Prevention of Dementia by Intensive Vascular Care (preDIVA) is a cluster-RCT evaluating the effect of 6-8 years of nurse-led intensive vascular care on incident dementia in community-dwelling older people aged 70-78 years.[16] Overall, no preventive effect of the intervention was found. The intervention seemed more beneficial in a subgroup with untreated hypertension who adhered to the intervention. As the preDIVA intervention targets several vascular risk factors, our hypothesis was that a risk score capturing several modifiable risk factors may function even better at selecting those responsive to the intervention.

Hence, our aim was to study whether a multi-domain intervention can prevent all-cause dementia and cognitive decline in older people across three different levels of a modifiable dementia risk score.

METHODS

The current study is a post hoc analysis in the preDIVA trial, which was previously published. [16] In short, the intervention comprised four-monthly visits to a practice nurse who gave individually tailored lifestyle advice on smoking, diet, physical activity, weight and blood

pressure (BP). If indicated, pharmacological treatment was started or optimized according to the prevailing guidelines on cardiovascular risk management.[106] The control condition was standard care. All community-dwelling older people aged 70-78 years registered at participating Dutch general practices were invited to participate. The only exclusion criteria were a diagnosis of dementia and/or any condition likely to hinder long-term follow-up (such as terminal illness or alcoholism). The trial is registered at the International Standard Randomized Controlled Trial Number registry (ISRCTN29711771).

LIBRA index

The LIBRA index has been designed based on a systematic review and Delphi consensus and has been validated in several cohorts, among which a cohort aged 70-79 years.[12,121,122] In preDIVA, ten out of 12 LIBRA factors were measured at baseline (Table 1). Similar to one of the previously mentioned validation studies,[122] there was no information on cognitive activity or adherence to the Mediterranean diet. Data on medical history, medication use, history of smoking and alcohol use were self-reported and cross-referenced with the electronic medical record of the general practitioner. BP, weight and height (to calculate Body Mass Index [BMI]) were measured using standard protocols. A blood sample was drawn to measure cholesterol and creatinine levels. The 15-item Geriatric Depression Scale was used to measure depressive symptoms and the LASA Physical Activity Questionnaire for physical activity.[123,124] The measures corresponding to the ten LIBRA items (Table 1) were aligned to the previously published validation studies.[121,122] Each item was assigned the appropriate score (Table 1) and the sum of these items formed the LIBRA index (with a maximum potential range of -1.0 to +12.7). Only participants with all ten items available to calculate the LIBRA index were included in the analysis. For a secondary analysis, the LIBRA index was extended with the non-modifiable risk factors age, sex and education (Table 1), in order to make it more comparable to other available dementia risk indices.[125] This was also done in the previously published studies on the LIBRA index.[121,122]

Primary and secondary outcomes

The primary outcome was all-cause dementia, according to the Diagnostic and Statistical Manual of Mental Disorders IV.[3] An independent outcome adjudication committee validated all dementia diagnoses, including a one-year follow-up period in incident cases to assure there were no false positive diagnoses. Cognition was the secondary outcome measure, which was measured every two years with the Mini-Mental State Examination (MMSE) and the Visual Association Test (VAT).[64,128] Participants attending at least one follow-up visit were included in the analyses on cognition.

Table 1 - Definition of risk/protective factors in the LIBRA index and corresponding scores [122]

	Definition	Score
Modifiable risk factors		
Depression	Score ≥5 on the 15-item Geriatric Depression Scale	+2.1
Hypertension	SBP ≥140 mmHg, DBP ≥90 mmHg and/or use of antihypertensive medication	+1.6
Obesity	BMI ≥30	+1.6
Smoking	Current smoker	+1.5
Hypercholesterolemia	Total cholesterol ≥6.2 mmol/L or use of cholesterol lowering medication	+1.4
Diabetes	Diabetes mellitus[a]	+1.3
Renal dysfunction	Estimated glomerular filtration rate <60 ml/min/1.73 m^2 [b]	+1.1
Physical inactivity	Not fulfilling the world health organisation criteria for physical activity as measured with the LASA Physical Activity Questionnaire[c]	+1.1
Coronary heart disease	Cardiovascular disease (defined as myocardial infarction, angina or peripheral arterial disease)[a]	+1.0
Low/moderate alcohol use	Alcohol use 1-14 units per week for males and 1-7 for females [126]	-1.0
Non-modifiable risk factors		
Age	Males: 70-74 years	+5.2
	Male: 75-78 years	+6.8
	Females: 70-74 years	+6.2
	Female: 75-78 years	+9.2
Education	High ≥13 years	0
	Medium 7-13 years	+1.4
	Low ≤7 years	+2.7

[a] Data were self-reported and cross-checked with electronic health records. [b] Estimated Glomerular Filtration rate was calculated with the creatinine-based Chronic Kidney Disease - Epidemiology Collaboration equation [127]. [c] The world health organisation criteria for physical activity are defined as ≥150 minutes/week moderate-intensity or ≥75 minutes/week vigorous-intensity or an equivalent combination. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BMI, body-mass index; TIA, transient ischemic attack.

Statistical analysis

We first assessed the association between the LIBRA index in the preDIVA population and incident dementia with Cox proportional hazards regression. We then divided the study population into participants with a low, intermediate and high LIBRA index based on tertiles of the index.[122] In each group, the crude effect of the intervention on all-cause dementia was assessed with Cox proportional hazards regression (model 1). The years from randomisation to dementia diagnosis or censoring date were used as timescale. To assess whether the LIBRA index is more useful as selection tool when containing both modifiable and major non-modifiable risk factors, we repeated our analysis with the LIBRA

index expanded with education (model 2) and additionally with age and sex (model 3).[122] As history of coronary heart disease is not modifiable, we removed it from the LIBRA index in a sensitivity analysis (model 4). Our primary analysis was crude and in a secondary analysis we adjusted for baseline imbalances between the intervention and control group. We also assessed the effect of adjusting for education as this is an important risk factor for dementia and is associated with many of the risk/protective factors included in the LIBRA index.[10] The proportional hazards assumption was tested using Schoenfeld residuals and was assessed graphically.[66]

Because of the cluster-randomised design we additionally performed a multi-level analysis to account for clustering within general practices and health-care centres. To account for competing risk of death, we assessed the intervention effect on mortality in the LIBRA groups, and, when appropriate, performed a competing risk analysis according to the cause-specific hazard method.[69] We added a per protocol analysis to assess whether the results were influenced by adherence to the intervention or control condition. In the per protocol analysis intervention participants were excluded who had on average less than two visits per year and inadvertent crossover control participants who had on average more than two visits per year. As the LIBRA index is more sensitive in a younger cohort,[122] we performed a predefined subgroup analysis on age (dichotomized at the median). In the primary preDIVA analyses, the intervention seemed to be effective in those with untreated hypertension who adhered to the intervention. However, the LIBRA definition of hypertension is rather crude (dichotomously defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg and/or use of antihypertensive medication). Therefore, we added subgroup analyses on World Health Organisation hypertension grades (that is; normotension, systolic BP <140 mmHg and/or diastolic BP <90 mmHg; grade I hypertension, systolic BP 140-160 mmHg and/or diastolic BP 90-100 mmHg; grade II or III hypertension, systolic BP ≥160 mmHg and/or diastolic BP ≥100 mmHg) and use of antihypertensive medication.[31] In the Netherlands, people with a history of cardiovascular disease (CVD) and diabetes visit a practice nurse as part of standard care, potentially diluting an intervention effect.[107] We therefore added analyses in subgroups based on history of CVD and type 2 diabetes. To assess whether the intervention led to an improvement of cardiovascular risk factors, as proxy for treatment effect, we compared decline in systolic BP, BMI and total cholesterol between baseline and the last available follow-up visit, across the three LIBRA groups.

To assess whether individual changes in cognition vary over time between treatment group, we used a multilevel growth model stratified for participants with a low, intermediate and high LIBRA index.[129] In this linear mixed effect model each participant and time in years were considered random effects and a time*randomisation interaction variable was included. Since absolute values of MMSE and VAT, or logarithmic transformation of these values, were not normally distributed, change in MMSE/VAT since baseline, which was normally

distributed, was used as outcome variable in the model. We performed our analyses in R studio version 3.2 using the survival and nlme packages.[130]

RESULTS

Of the 3526 preDIVA participants at baseline, 3339 (94.7%) had all ten LIBRA items available at baseline and could be included in the analyses (Figure S1). Median LIBRA score at baseline was 3.1. Participants with the highest LIBRA index were slightly older (low 74.2 years, intermediate 74.3 years, high 74.5 years; p-value <0.01) and more often had a low education level (low 19.2%, intermediate 22.1%, high 29.9%; p-value <0.01; Table 2). Systolic BP was highest in the intermediate LIBRA group (low 151.5 mmHg, intermediate 157.5 mmHg, high 156.7 mmHg; p-value <0.01). The baseline characteristics of the intervention and control group within each LIBRA group were well balanced, except for small differences in total cholesterol (respectively, 5.3 versus 5.5 mmol/L; p-value 0.03) in the intermediate LIBRA group, and mean systolic BP (157.9 versus 155.3 mmHg; p-value 0.04) and sex (37.3% versus 44.2%; p-value 0.02) in the high LIBRA group (Table S1).

All-cause dementia was diagnosed in 220 (6.7%) participants; 76 of 1091 (7.0%) participants with a low LIBRA index, 71 of 1081 (6.6%) with an intermediate LIBRA index and 73 of 1102 (6.6%) with a high LIBRA index. The LIBRA index (model 1) was not associated with incident dementia (crude hazard ratio [HR] 1.02 per point increase in LIBRA index, 95% confidence interval [CI] 0.96-1.09). Adding education to the LIBRA index (model 2) did not change these results (HR 1.06; 95% CI 0.90-1.24). The LIBRA index including education, age and sex (model 3) was significantly associated with incident dementia (HR 1.07, 95% CI 1.02-1.12).

The HR of the effect of intensive vascular care on incident all-cause dementia was 0.71 (95% CI 0.45-1.12) in the low, 1.06 (95% CI 0.66-1.69) in the intermediate and 1.02 (95% CI 0.64-1.62) in the high LIBRA group (model 1; Figure 1; Table 3). The interaction between randomisation and LIBRA index divided in tertiles was not significant. Also, when including age, sex and education (model 2 and 3) or excluding coronary heart disease (model 4) in the LIBRA index and stratifying our study population based on this modified LIBRA index, the intervention was not effective in any of the groups (Table 3). Adjustment for baseline imbalances or education did not significantly influence the results, nor did accounting for clustering within general practices and health-care centres (Table S2). The results were similar in the per protocol analysis (Table S2). Mortality risk increased with increasing LIBRA index, but the intervention effect on mortality was not significantly different in the LIBRA risk groups (Table S3). In all secondary analyses, the HR was lowest, albeit non-significant, in participants with the lowest LIBRA index (Table S2). Subgroup analyses showed a significant interaction (p-value 0.03) between age and randomisation in the intermediate LIBRA group with a lower HR in younger participants aged <74.3 years (HR 0.55; 95% 0.26-1.17) compared

Table 2 - Baseline characteristics by LIBRA group

	Low LIBRA index	Intermediate LIBRA index	High LIBRA index	P-value
Total number of participants	1091	1081	1102	
Range in LIBRA index	-1.0 to 2.6	2.6 to 4.2	4.2 to 11.6	
Demographics				
Age (years)	74.2 (SD 2.5)	74.3 (SD 2.5)	74.5 (SD 2.5)	<0.01
Sex (male)	528 (48.4%)	519 (48.0%)	445 (40.4%)	<0.01
Education				<0.01
Low (<7 years)	209 (19.2%)	239 (22.1%)	330 (29.9%)	
Medium (7-12 years)	695 (63.7%)	671 (62.1%)	660 (59.9%)	
High (>12 years)	179 (16.4%)	161 (14.9%)	101 (9.2%)	
Race (white)	1057 (96.9%)	1042 (96.4%)	1054 (95.6%)	<0.01
Medical history				
CVD (excl. stroke or TIA)	66 (6.0%)	372 (34.4%)	526 (47.7%)	<0.01
Stroke or TIA	60 (5.5%)	95 (8.8%)	169 (15.3%)	<0.01
Cardiovascular risk factors				
Systolic BP (mmHg)	151.5 (SD 22.0)	157.5 (SD 20.8)	156.7 (SD 20.6)	<0.01
Diastolic BP (mmHg)	81.0 (SD 10.9)	82.0 (SD 10.9)	81.3 (SD 11.0)	0.09
Total cholesterol (mmol/L)	5.4 (SD 0.9)	5.4 (SD 1.1)	4.9 (SD 1.2)	<0.01
LDL cholesterol (mmol/L)	3.3 (SD 0.8)	3.2 (SD 1.0)	2.8 (SD 1.0)	<0.01
Body mass index (kg/m^2)	25.9 (SD 3.1)	26.7 (SD 3.6)	29.6 (SD 4.6)	<0.01
Type 2 diabetes	30 (2.7%)	103 (9.5%)	460 (41.7%)	<0.01
Smoking (currently)	46 (4.2%)	113 (10.5%)	265 (24.0%)	<0.01
Alcohol use (units/week)	3 [0-7]	4 [0-14]	0 [0-10]	<0.01
Physically active (WHO)	1065 (97.6%)	990 (91.6%)	784 (71.1%)	<0.01
Creatinine (umol/L)	77 [68-88]	80 [68-93]	82 [71-97]	<0.01
Medication use				
Antihypertensive medication	332 (30.4%)	631 (58.4%)	838 (76.0%)	<0.01
Cholesterol lowering medication	77 (7.1%)	370 (34.2%)	664 (60.3%)	<0.01
Disability and neuropsychiatric assessment				
Mini-mental State Examination (MMSE)	29 [28-30]	28,5 [27-29]	28 [27-29]	<0.01
Visual Association Test (VAT)	6 [5-6]	6 [5-6]	6 [5-6]	0.05
Geriatric Depression Scale (GDS)	1 [0-1]	1 [0-2]	2 [0-4]	<0.01

Data are presented as number (percentage), mean (standard deviation) or median [interquartile range]. CVD indicates cardiovascular disease; excl., excluding; TIA, transient ischemic attack; BP, blood pressure; LDL, low-density lipoprotein; WHO, world health organisation.

Table 3 - Intervention effect on incident all-cause dementia across the models, by LIBRA group

	LIBRA group	Intervention (n,%)	Control (n,%)	Hazard ratio (95% CI)	p-for interaction
Model 1 – LIBRA index	Low	33/567 (5.8%)	43/524 (8.2%)	0.71 (0.45-1.12)	Ref
	Intermediate	39/576 (6.8%)	32/505 (6.3%)	1.06 (0.66-1.69)	0.23
	High	41/606 (6.8%)	32/496 (6.5%)	1.02 (0.64-1.62)	0.27
Model 2 – LIBRA index including education	Low	28/555 (5.0%)	39/498 (7.8%)	0.64 (0.40-1.05)	Ref
	Intermediate	38/525 (7.2%)	31/482 (6.4%)	1.11 (0.69-1.79)	0.12
	High	46/660 (7.0%)	35/525 (6.7%)	1.03 (0.66-1.59)	0.17
Model 3 – LIBRA index including age, sex & education	Low	32/564 (5.7%)	33/515 (6.4%)	0.88 (0.54-1.43)	Ref
	Intermediate	35/568 (6.2%)	34/510 (6.7%)	0.91 (0.57-1.47)	0.94
	High	45/608 (7.4%)	38/480 (7.9%)	0.92 (0.59-1.41)	0.92
Model 4 – LIBRA index excluding coronary heart disease	Low	36/559 (6.0%)	45/559 (8.1%)	0.75 (0.48-1.16)	Ref
	Intermediate	35/570 (6.1%)	28/477 (5.9%)	1.05 (0.64-1.72)	0.32
	High	42/580 (7.2%)	34/489 (7.0%)	1.01 (0.64-1.59)	0.34

CI indicates confidence interval; ref, reference category

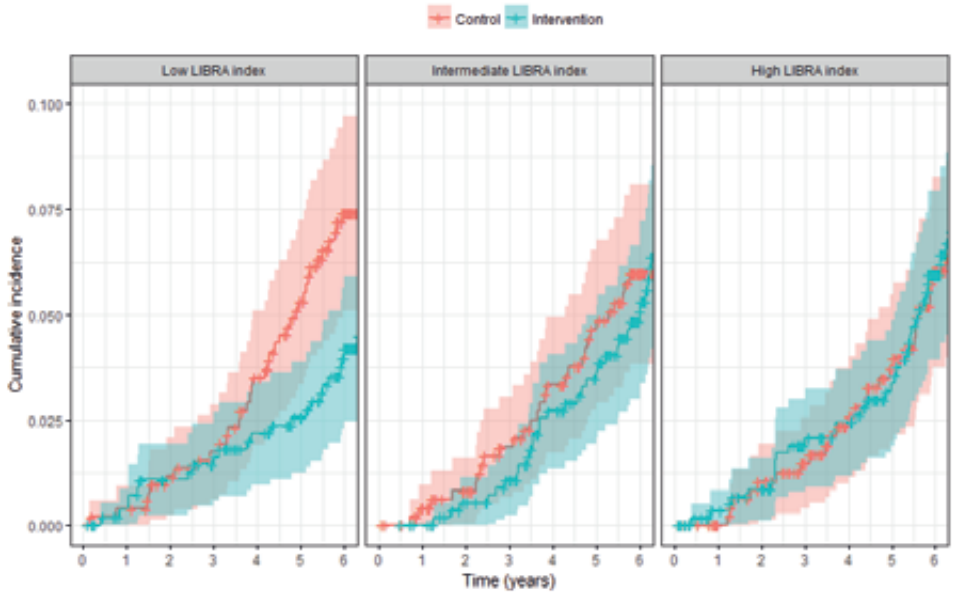

Figure 1 - Cumulative incidence curves of the risk of dementia comparing intervention and control group in participants with a low, intermediate and high LIBRA index

The line indicates the incidence and the shaded area the 95% confidence interval. The number of participants at risk at 6 years follow-up were 791 in the low LIBRA group (408 intervention; 383 control), 756 in the intermediate LIBRA group (400 intervention; 356 control) and 738 in the high LIBRA group (406 intervention, 332 control).

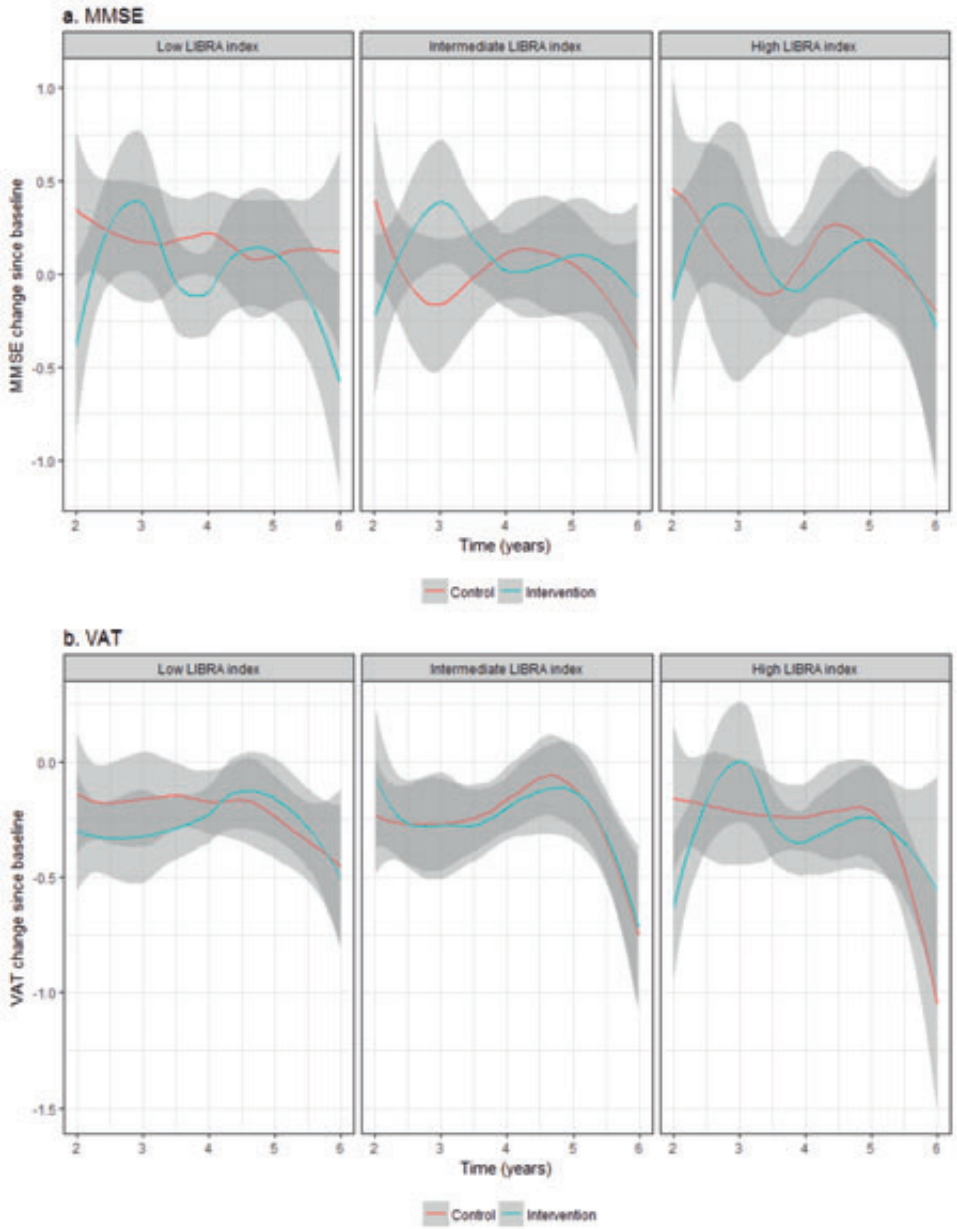

Figure 2 - Effect of the intervention on MMSE (a) and VAT (b) change since baseline in the LIBRA groups

Trajectories of change in MMSE and VAT since baseline comparing control (red line) to intervention (blue line) group in each LIBRA group, as predicted with the multilevel growth model. A positive value indicates an increase in MMSE/VAT since baseline, while a negative value indicates decrease. MMSE indicates mini-mental state examination; VAT, visual association test.

to older participants (HR 1.65; 95% CI 0.88-3.09) (Table S4). We found an interaction with diabetes in the high LIBRA group (p-value 0.03), with a lower HR in participants with diabetes (HR 0.61; 95% CI 0.32-1.15) in comparison to those without (HR 1.78; 95% CI 0.87-3.64). We found no other interactions in the subgroup analyses. Participants with a higher LIBRA index had on average more decline in systolic BP (respectively in the low, intermediate and high LIBRA group; -2.3, -5.9, -5.8; p-value <0.01), less decline in total cholesterol (-0.3, -0.3, -0.1; p-value <0.01) and more decline in BMI (-0.5, -0.5, -0.9; p-value <0.01). The intervention led to a significant decline in systolic BP in the low (intervention vs control; -3.9 vs. -0.5; p-value 0.03) and intermediate LIBRA group (-7.4 vs. -4.2; p-value 0.04), but not in the high LIBRA group (-7.1 vs. -4.3; p-value 0.09; Table S5). The intervention did not significantly reduce cholesterol or BMI in any of the LIBRA groups (Table S5).

2674 participants had at least one valid MMSE score and 2671 at least one valid VAT score after baseline and could be included in the analyses on cognitive decline (Figure e-1). Participants excluded from these analyses were on average older, had a higher cardiovascular risk and a lower baseline MMSE and VAT (Table S6). After three years, decline in MMSE did not significantly differ between the intervention and control group among participants with a low (mean difference [MD] -0.08; 95% CI -0.28 to 0.13), intermediate (MD 0.07; 95% CI -0.14 to 0.27) or high LIBRA index (MD -0.06; 95% CI -0.30 to 0.18; Figure 2a, Table S7). Decline in VAT also did not differ between treatment groups in the low (MD 0.03; 95% CI -0.09 to 0.14), intermediate (MD -0.04; 95% CI -0.16 to 0.08) or high LIBRA group (MD 0.07; 95% CI -0.05 to 0.19; Figure 2b, Table S7).

DISCUSSION

In the preDIVA study population, aged 70-78 years, the LIBRA index did not identify a high-risk group in whom the multi-domain intervention was effective in preventing dementia or cognitive decline. On the contrary, there was a trend for a preventive effect in the subgroup with a low LIBRA index. Results were comparable when including non-modifiable risk factors in the LIBRA index.

The concept of selecting people at increased risk of dementia for preventive interventions to magnify the intervention effect is widely supported among experts in the field and has been incorporated in the design of recent multi-domain prevention trials.[14,15] Our results do not support this strategy, and are even in contrast with this concept, at least in later life, suggesting a more favourable effect of the intervention in those with a low LIBRA index. A potential explanation for this is that the contrast between the intervention and control condition was too small, partly due to Hawthorne effects and improvements in the standard care for cardiovascular risk management during the trial.[16] Although in participants with a higher LIBRA index a greater reduction in systolic BP could be achieved this was the case in

both the intervention and control group and the difference between the treatment groups was smallest in the high LIBRA group. Another potential explanation for our results is that the LIBRA index does not successfully classify dementia risk in this older population aged 70-78 years. Indeed, our analyses did not show an association between a high LIBRA index and increased risk of dementia. Since preDIVA is an RCT, this could potentially (partly) be due to the fact that the dementia risk was influenced during the trial by the intervention and/or Hawthorne effects. For example systolic blood pressure decreased by approximately 8 mmHg in the intervention group and 4 mmHg in the control group, and the decline was steepest in participants with hypertension at baseline.[16] In one of the LIBRA validation studies, a higher LIBRA index was associated (at group level) with an increased risk of dementia in people aged 70-79 years.[122] The individual predictive accuracy in late life was, however, poor, with a C statistic of 0.50, and seemed to decrease with increasing age. Investigating the utility of the LIBRA index as selection tool for prevention trials at a younger age (55-70 years) may yield different results. A third potential explanation is that the factors in the LIBRA index and in other dementia risk scores are dichotomous and not designed to precisely quantify the magnitude of the risk/protective factor nor the room for improvement. For example, the potential for improvement is different for someone with a systolic BP of 125 mmHg on antihypertensive medication compared to a person with a systolic BP of 155 mmHg without medication, although both are weighted equally in the LIBRA index with the dichotomous score for hypertension (including both high BP and/or antihypertensive medication use). In order for a risk estimation tool to be useful for selection of high-risk populations for dementia prevention trials, the potential for improvement should be taken into account (for example by distinguishing treated or untreated hypertension).

Regardless of the LIBRA index performance in high age populations, the concept of selecting people at high risk of dementia may be appropriate for younger people (that is, <70 years) only. In older people at high risk of dementia, cerebrovascular and neurodegenerative damage may already be irreversible, while those with a low risk could still benefit from risk factor improvement in order to maintain cognitive function. Also, several observational studies have shown a diminishing or even inverting association between risk factors and incident dementia in older people, as for example the J-shaped relation with BP.[20] Therefore, future trials should perhaps either focus on people with lowest dementia risk in old age or highest dementia risk in midlife. This would, however, imply that substantially larger sample sizes or longer follow-up will be required, as incidence rates in these groups are lower.

A strength of this analysis is that preDIVA is, up until now, the only multi-domain prevention trial with dementia as primary outcome. The population-based approach with few exclusion criteria renders preDIVA a suitable study to test whether the LIBRA-index is a promising tool to select high-risk groups from the general population. A limitation is the overall neutral result of the preDIVA trial, perhaps limiting the possibility to detect high-

risk groups who benefit most. However, a significant effect of the intervention was found in the per protocol analysis among participants with untreated hypertension at baseline (HR 0.54, 95% CI 0.32-0.92),[16] while the results of the present analyses do not show a trend towards improved treatment effects in higher LIBRA groups. Another limitation is that no other neuropsychological tests were performed besides the MMSE and VAT to detect more subtle cognitive changes. We did not have information on two of the 12 LIBRA items, among which cognitive activity which is the strongest-weighted item in the LIBRA index.[121] These factors were, however, already identified as risk factors that need further validation in the systematic review and Delphi consensus used to design the LIBRA index and were also not included the validation study among people at late life (70-79 years).[12,122] Furthermore, it may be argued that cognitive activity at this age is not as much a modifiable risk factor but rather an early indicator of developing cognitive decline and dementia.[131]

CONCLUSIONS

Within our study population of community-dwelling people aged 70-78 years, a modifiable dementia risk score does not identify heterogeneity in treatment effect of a multi-domain intervention to prevent dementia or cognitive decline. It suggests that in older adults a high LIBRA index may not be a suitable parameter to select participants for a dementia prevention trial. Specific characteristics of the preDIVA study, including the overall neutral effect of the intervention and relatively high age-group may have contributed to the lack in discriminating capacity of the LIBRA index.

SUPPLEMENTARY MATERIAL

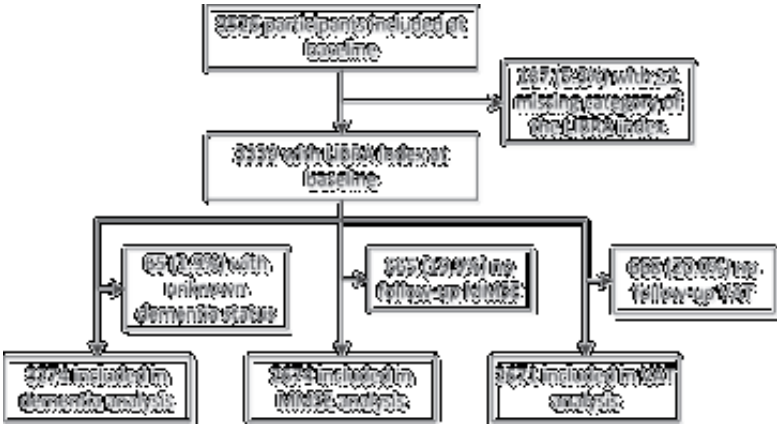

Figure S1 - Flow diagram

LIBRA indicates lifestyle for brain health; MMSE, mini-mental state examination; VAT, visual association test.

Table S1 - Baseline characteristics per randomisation group and LIBRA risk group

	Low LIBRA index (N=1091)			Intermediate LIBRA index (N=1081)			High LIBRA index (N=1102)		
	Control	Intervention	P	Control	Intervention	P	Control	Intervention	P
Demographics									
Age (years)	74.2 (SD 2.5)	74.1 (SD 2.5)	0.50	74.4 (SD 2.5)	74.3 (SD 2.4)	0.52	74.4 (SD 2.51	74.5 (SD 2.43	0.58
Gender (male)	258 (49.2%)	270 (47.6%)	0.62	236 (46.7%)	283 (49.1%)	0.46	219 (44.2%)	226 (37.3%)	0.02
Education			0.59			1.00			0.36
Low (<7 yr)	95 (18.1%)	114 (20.1%)		112 (22.2%)	127 (22.0%)		145 (29.2%)	185 (30.5%)	
Medium (7-12 yr)	340 (64.9%)	355 (62.6%)		314 (62.2%)	357 (62.0%)		290 (58.5%)	370 (61.1%)	
High (>12 yr)	82 (15.6%)	97 (17.1%)		75 (14.9%)	86 (14.9%)		52 (10.5%)	49 (8.1%)	
Race (white)	550 (97.0%)	507 (96.8%)	1.00	549 (95.3%	493 (97.6%)	0.24	582 (96.0%)	472 (95.2%)	0.59
Medical history									
CVD (excl. stroke or TIA)	36 (6.9%)	30 (5.3%)	0.31	167 (33.1%)	205 (35.6%)	0.40	240 (48.4%)	286 (47.2%)	0.72
Stroke or TIA	30 (5.7%)	30 (5.3%)	0.79	45 (8.9%)	50 (8.7%)	0.91	85 (17.1%)	84 (13.9%)	0.15
Cardiovascular risk factors									
SBP (mmHg)	150.8 (SD 20.6)	152.2 (SD 23.3)	0.29	156.6 (SD 20.7)	158.3 (SD 20.9)	0.18	155.3 (SD 19.7)	157.9 (SD 21.2)	0.04
DBP (mmHg)	81.0 (SD 10.2)	81.0 (SD 11.4)	1.00	81.9 (SD 10.9)	82.0 (SD 10.8)	0.84	81.3 (SD 10.9)	81.3 (SD 11.1)	0.92
Total cholesterol (mmol/L)	5.4 (SD 0.9)	5.4 (SD 0.9)	0.48	5.5 (SD 1.1)	5.3 (SD 1.1)	0.03	4.9 (SD 1.2)	4.9 (SD 1.2)	0.62
LDL cholesterol (mmol/L)	3.2 (SD 0.8)	3.3 (SD 0.8)	0.42	3.1 (SD 1.0)	3.3 (SD 1.0)	0.05	2.7 (SD 1.0)	2.8 (SD 1.1)	0.12
BMI (kg/m^2)	25.9 (SD 3.1)	26.0 (SD 3.1)	0.47	26.7 (SD 3.6)	26.8 (SD 3.7)	0.71	29.5 (SD 4.61)	29.7 (SD 4.6)	0.56
Type 2 diabetes	12 (2.3%)	18 (3.2%)	0.47	47 (9.3%)	56 (9.7%)	0.83	206 (41.5%)	254 (41.9%)	0.91
Smoking (currently)	20 (3.8%)	26 (4.6%)	0.52	53 (10.5%)	60 (10.4%)	1.00	120 (24.2%)	145 (23.9%)	0.94
Alcohol use (units/week)	3 [0-8]	3 [0-7]	0.87	4 [0-14]	4 [0-14]	0.70	1 [0-10]	0 [0-12]	0.55
Physically active (WHO)	550 (97.0%)	515 (98.3%)	0.21	531 (92.2%)	459 (90.9%)	0.52	424 (70%)	360 (72.6%)	0.36
Creatinine (umol/L)	76 [68-88]	77 [68-88]	0.98	79 [67-93]	80 [69-93]	0.35	81 [70-97]	82 [72-97]	0.41

Table S1 - Continued

	Low LIBRA index (N=1091)			Intermediate LIBRA index (N=1081)			High LIBRA index (N=1102)		
	Control	Intervention	P	Control	Intervention	P	Control	Intervention	P
Medication use									
Antihypertensive med.	161 (30.7%)	171 (30.2%)	0.84	310 (61.4%)	321 (55.7%)	0.08	384 (77.4%)	454 (74.9%)	0.38
Cholesterol lowering med.	38 (7.3%)	39 (6.9%)	0.82	171 (33.9%)	199 (34.5%)	0.81	299 (60.3%)	365 (60.2%)	1.00
Disability and neuropsychiatric assessment									
MMSE	29 [28-29]	29 [27-30]	0.58	29 [27-29]	28 [27-29]	0.99	28 [27-29]	28 [27-29]	0.44
VAT	6 [5-6]	6 [5-6]	0.60	6 [5-6]	6 [5-6]	0.62	6 [5-6]	6 [5-6]	0.20
GDS	1 [0-1]	1 [0-2]	0.44	1 [0-2]	1 [0-2]	0.67	2 [0-4]	2 [0-4]	0.27

Data are presented as number (percentage), mean (standard deviation) or median [interquartile range]. Yr indicates years; CVD, cardiovascular disease; excl., excluding; TIA, transient ischemic attack; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low-density lipoprotein; BMI, body-mass index; WHO, world health organisation; med., medication; MMSE, mini-mental state examination; VAT, visual association test; GDS, geriatric depression scale.

Table S2 - Secondary analyses

		Intervention (n,%)	Control (n,%)	Hazard ratio (95% CI)	p-for interaction
Adjusting for total cholesterol	Low	33/567 (5.8%)	43/524 (8.2%)	0.71 (0.45-1.12)	Ref
	Intermediate	39/576 (6.8%)	32/505 (6.3%)	1.05 (0.66-1.68)	0.24
	High	41/606 (6.8%)	32/496 (6.5%)	1.01 (0.64-1.60)	0.27
Adjusting for mean systolic BP	Low	33/567 (5.8%)	43/524 (8.2%)	0.72 (0.46-1.13)	Ref
	Intermediate	39/576 (6.8%)	32/505 (6.3%)	1.06 (0.66-1.69)	024
	High	41/606 (6.8%)	32/496 (6.5%)	1.04 (0.65-1.65)	0.26
Adjusting for gender	Low	33/567 (5.8%)	43/524 (8.2%)	0.71 (0.45-1.12)	Ref
	Intermediate	39/576 (6.8%)	32/505 (6.3%)	1.06 (0.66-1.69)	0.24
	High	41/606 (6.8%)	32/496 (6.5%)	1.01 (0.63-1.60)	0.27
Adjusting for education	Low	33/567 (5.8%)	43/524 (8.2%)	0.70 (0.44-1.10)	Ref
	Intermediate	39/576 (6.8%)	32/505 (6.3%)	1.03 (0.64-1.65)	0.25
	High	41/606 (6.8%)	32/496 (6.5%)	105 (0.66-1.69)	0.21
Accounting for clustering*	Low	33/567 (5.8%)	43/524 (8.2%)	0.71 (0.45-1.13)	Ref
	Intermediate	39/576 (6.8%)	32/505 (6.3%)	1.06 (0.66-1.69)	0.22
	High	41/606 (6.8%)	32/496 (6.5%)	1.05 (0.64-1.72)	0.26
Per-protocol analysis	Low	24/429 (5.6%)	41/480 (8.5%)	0.62 (0.37-1.02)	Ref
	Intermediate	24/452 (5.3%)	32/466 (6.9%)	0.71 (0.42-1.21)	0.73
	High	30/443 (6.8)	29/463 (6.3%)	1.02 (0.61-1.71)	0.17

** Clusters were* general practices and health-care centres. *The p-for interaction indicates the p-value of the interaction variable intervention*LIBRA group. The p-for interaction for the intermediate LIBRA group compares the low with the intermediate LIBRA group; the p-for interaction for the high LIBRA group compares the low with the high LIBRA group. CI indicates confidence interval; Ref, reference category; BP, blood pressure.*

Table S3 - Competing risk analysis

	Dementia-free survival (CSHR, 95% CI)	Mortality (CSHR, 95% CI)	Dementia (CSHR, 95% CI)	Dementia (SHR, 95% CI)
Low risk	1.04 (0.91-1.19)	1.07 (0.74-1.56)	0.71 (0.45-1.12)	0.70 (0.44-1.10)
Intermediate risk	0.94 (0.83-1.08)	1.12 (0.81-1.54)	1.06 (0.66-1.69)	1.06 (0.67-1.70)
High risk	0.95 (0.83-1.09)	0.87 (0.68-1.12)	1.03 (0.65-1.63)	1.05 (0.66-1.67)

CSHR indicates cause specific hazard ratio, an estimate for the direct effect of the intervention on survival, mortality or dementia. SHR indicates subdistribution hazard ratio, an estimate for the risk of dementia while accounting for mortality as competing event. This is done by giving every participant with no diagnosis of dementia the longest follow-up duration instead censoring them at time of death or lost to follow-up.

Table S4 - Subgroup analyses on age, hypertension grade, antihypertensive medication, history of cardiovascular disease and diabetes

	Low risk			Intermediate risk			High risk		
	N=	HR (95% CI)	p-for int.	N=	HR (95% CI)	p-for int.	N=	HR (95% CI)	p-for int.
Age <74.3 year	584	0.96 (0.44-2.10)	Ref	554	0.55 (0.26-1.17)	Ref	541	1.13 (0.52-2.47)	Ref
Age ≥74.3 year	526	0.63 (0.36-1.11)	0.40	546	1.65 (0.88-3.09)	0.03	588	0.95 (0.54-1.69)	0.73
Normotension	366	0.90 (0.44-1.82)	Ref	184	1.07 (0.24-4.77)	Ref	209	0.92 (0.34-2.45)	Ref
Grade I hypertension	364	0.53 (0.20-1.40)	0.37	451	1.00 (0.50-2.01)	0.72	454	1.01 (0.48-2.09)	0.87
Grade II or III hypertension	380	0.59 (0.27-1.28)	0.43	465	1.05 (0.52-2.13)	0.74	466	1.18 (0.55-2.51)	0.71
AHM	337	1.01 (0.48-2.16)	Ref	642	1.12 (0.62-2.04)	Ref	858	1.01 (0.59-1.70)	Ref
No AHM	770	0.58 (0.33-1.04)	0.27	457	0.91 (0.42-1.98)	0.64	270	1.06 (0.40-2.78)	0.93
History of CVD	123	0.87 (0.24-3.16)	Ref	661	1.25 (0.62-2.53)	Ref	508	0.82 (0.44-1.53)	Ref
No history of CVD	981	0.68 (0.42-1.12)	0.79	431	0.91 (0.47-1.75)	0.53	614	1.32 (0.65-2.69)	0.32
Diabetes	30	NA		104	0.77 (0.22-2.69)	Ref	470	0.61 (0.32-1.15)	Ref
No diabetes	1080	NA		996	1.12 (0.68-1.87)	0.49	659	1.78 (0.87-3.64)	0.03

*History of cardiovascular disease is defined as a previous diagnosis of myocardial infarction, angina, stroke, TIA and/or peripheral arterial disease. P for int. indicates the p-value for the interaction variable intervention*subgroup. Diabetes subgroup analysis could not be performed in the low LIBRA group, as numbers were too small. Ref indicates the reference category; AHM, antihypertensive medication; NA, not applicable.*

Table S5 - Treatment effect on vascular risk factors in the LIBRA groups

	Low risk			Intermediate risk			High risk		
	Intervention	Control	p-value	Intervention	Control	p-value	Intervention	Control	p-value
SBP (mmHg)	-3.9 (23.4)	-0.5 (21.9)	0.03	-7.4 (24.2)	-4.2 (21.7)	0.04	-7.1 (25.5)	-4.3 (22.8)	0.09
Cholesterol (mmol/L)	-0.4 (0.9)	-0.3 (0.9)	0.11	-0.3 (1.1)	-0.4 (1.0)	0.07	-0.12 (1.0)	-0.17 (1.1)	0.54
BMI (kg/m²)	-0.5 (4.2)	-0.5 (2.8)	0.82	-0.5 (2.7)	-0.6 (2.8)	0.47	-1.0 (3.9)	-0.8 (3.7)	0.64

Data presented are mean (SD) change in systolic BP, BMI or cholesterol between baseline and the last available follow-up visit, comparing the intervention to the control group. BP indicates blood pressure; BMI, body mass index.

Table S6 - Baseline characteristics of participant in- and excluded in the cognitive analyses

	Included in analyses (N= 2674)	Excluded from analyses (N= 665)	P-value
Demographics			
Age (years)	74.2 (SD 2.4)	74.8 (SD 2.5)	<0.01
Sex (male)	1214 (45.4%)	310 (46.6%)	0.60
Education			<0.01
Low (<7 years)	596 (22.3%)	195 (29.3%)	
Medium (7-12 years)	1690 (63.2%)	375 (56.4%)	
High (>12 years)	367 (13.7%)	86 (12.9%)	
Race (white)	2577 (96.4%)	641 (96.4%)	0.35
Medical history			
CVD (excl. stroke or TIA)	763 (28.5%)	228 (34.3%)	<0.01
Stroke or TIA	257 (9.6%)	76 (11.4%)	0.15
Cardiovascular risk factors			
Systolic BP (mmHg)	154.7 (SD 21.0)	157.7 (SD 22.7)	<0.01
Diastolic BP (mmHg)	81.3 (SD 10.7)	82.0 (SD 11.8)	0.21
Total cholesterol (mmol/L)	5.3 (SD 1.1)	5.2 (SD 1.1)	0.03
LDL cholesterol (mmol/L)	3.1 (SD 1.0)	3.0 (SD 0.9)	0.04
Body mass index (kg/m^2)	27.4 (SD 4.2)	27.4 (SD 4.2)	0.96
Type 2 diabetes	502 (18.8%)	102 (15.3%)	0.04
Smoking (currently)	334 (12.5%)	105 (15.8%)	0.02
Alcohol use (units/week)	3 [0-10]	2 [0-10]	0.09
Physically active (WHO)	2353 (88%)	543 (81.7%)	<0.01
Creatinine (umol/L)	79 [69-92]	81 [70-94]	0,0308
Medication use			
Antihypertensive medication	1466 (54.8%)	371 (55.8%)	0.65
Cholesterol lowering medication	905 (33.8%)	228 (34.3%)	0.85
Disability and neuropsychiatric assessment			
Mini-mental State Examination (MMSE)	29 [27-29]	28 [27-29]	<0.01
Visual Association Test (VAT)	6 [5-6]	6 [5-6]	<0.01
Geriatric Depression Scale (GDS)	1 [0-2]	1 [0-3]	<0.01

Participants are excluded from the analyses on cognitive decline if they only had one MMSE/VAT. Data are presented as number (percentage), mean (standard deviation) or median [interquartile range]. CVD indicates cardiovascular disease; excl., excluding; TIA, transient ischemic attack; BP, blood pressure; LDL, low-density lipoprotein; WHO, world health organisation.

Table S7 - Treatment effect on cognitive decline since baseline in the LIBRA risk groups

		Low LIBRA index (beta, 95% CI)	Intermediate LIBRA index (beta, 95% CI)	High LIBRA index (beta, 95% CI)
MMSE decline	Intercept (at 3 years follow-up)	0.09 (-0.06 to 0.24)	0.00 (-0.15 to 0.14)	0.00 (-0.18 to 0.17)
	Randomisation	-0.08 (-0.28 to 0.13)	0.07 (-0.14 to 0.27)	-0.06 (-0.30 to 0.18)
	Time (years)	-0.06 (-0.10 to -0.01)	-0.04 (-0.09 to 0.01)	-0.07 (-0.13 to -0.02)
	Randomisation * Time	0.01 (-0.05 to 0.07)	0.01 (-0.06 to 0.07)	0.03 (-0.05 to 0.10)
VAT decline	Intercept (at 3 years follow-up)	-0.22 (-0.30 to -0.14)	-0.28 (-0.37 to -0.19)	-0.25 (-0.34 to -0.16)
	Randomisation	-0.03 (-0.14 to 0.09)	0.04 (-0.08 to 0.16)	-0.07 (-0.19 to 0.05)
	Time (years)	-0.09 (-0.14 to -0.05)	-0.01 (-0.05 to 0.04)	-0.10 (-0.16 to -0.04)
	Randomisation * Time	0.05 (-0.01 to 0.12)	-0.08 (-0.15 to -0.01)	0.02 (-0.06 to 0.10)

*The intercept indicates the mean change in MMSE/VAT since baseline at 3 years follow-up for the control group. Randomisation indicates the mean difference in MMSE/VAT for the intervention compared to the control group at year 3 years. Time (years) indicates mean change in MMSE/VAT in the control group per year. The interaction term (Randomisation * Time) describes the difference in the effect of time for the intervention compared to the control group.*

OLDER EUROPEANS' REASONS FOR PARTICIPATING IN A MULTINATIONAL EHEALTH PREVENTION TRIAL

A CROSS-COUNTRY COMPARISON USING MIXED METHODS (ACCEPT-HATICE)

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Submitted

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ABSTRACT

Background Randomised controlled trials (RCTs) are challenging in older populations, and relatively uncommon, particularly those testing eHealth interventions. Better understanding of older adults' motivations for participating could improve recruitment and study design in future trials, thereby increasing their validity and facilitating intervention implementation.

Objective To explore older adults' reasons for participating in a multinational eHealth prevention trial, and compare motivations between countries.

Study design and setting Mixed methods research using quantitative (online questionnaire) and qualitative (semi-structured interviews) approaches in a sub-study conducted during the recruitment phase of an 18-month RCT testing the efficacy of an eHealth intervention for self-management of risk factors for cardiovascular disease (CVD) and cognitive decline in older adults in Finland, France and the Netherlands.

Subjects 343 dementia-free community-dwellers aged 65+ with basic computer literacy and either ≥2 cardiovascular risk factors or history of CVD/diabetes.

Results Contributing to scientific progress, wanting to improve one's lifestyle, and benefiting from additional medical monitoring were the predominant reasons for participating. Altruistic reasons were particularly relevant in France, while Finnish and Dutch participants mainly emphasised the benefits of lifestyle changes and regular medical check-ups. During interviews, preventing functional dependency emerged as a key underlying motivation. Some trial design features also influenced the decision to participate.

Conclusions Altruism and personal benefits motivated older adults to participate in the trial; emphasising such aspects could facilitate recruitment in future RCTs. Additional medical monitoring may be particularly appealing when access to public healthcare is considered limited.

INTRODUCTION

Given the unprecedented ageing of the global population,[132] there is an urgent need for strategies to encourage healthy ageing and prevent age-related disorders, such as cardiovascular disease (CVD) and dementia. Healthy lifestyle and successful management of cardiovascular risk factors are thought to play an important role in this regard,[11] but conclusive evidence and guidelines about effective and comprehensive interventions, particularly for dementia, are still lacking. Self-management could be a way to improve guideline adherence, and, with rising Internet use in older age-groups,[133] wide-reaching and cost-efficient eHealth interventions targeting CVD and dementia risk factors, and promoting a healthy lifestyle, could be an innovative tool to encourage this.[17]

Randomised controlled trials (RCTs), which are needed to demonstrate the efficacy of interventions, are challenging in older populations, not least because of difficulties with recruitment, which can threaten their validity.[134-136] Therefore, RCTs targeting this age-group are relatively uncommon,[137] particularly those testing eHealth interventions,[138] presumably because Internet use has traditionally been lower in this population.[133]

A better understanding of older adults' motivations for participating in RCTs could improve the design and recruitment of future trials, thus increasing the validity of their findings, and also facilitate the implementation of interventions at the population level. However, little is known about their opinions on and reasons for participating in RCTs,[135] particularly in the context of lifestyle-based prevention or eHealth trials. Furthermore, it is unclear whether motivations differ between countries, since previous studies have generally related to trials conducted in a single country.[137]

The primary aim of this analysis was, therefore, to explore older adults' reasons for participating in a European multinational eHealth prevention trial, and to compare motivations between countries. Furthermore, we aimed to specifically assess the influence of using an Internet intervention on the decision to participate in a prevention trial.

METHODS

Setting & participants

ACCEPT-HATICE was a mixed-methods sub-study of the 'Healthy Ageing Through Internet Counselling in the Elderly'(HATICE) trial (ISRCTN48151589). Quantitative and qualitative approaches were used in order to explore reasons for participating among our entire sample, and gain a comprehensive understanding of underlying motivations in a sub-sample. HATICE was an 18-month RCT testing the efficacy of an interactive Internet platform designed for older adults to improve the self-management of CVD risk factors for the prevention of CVD and cognitive decline.[17,18] Between March 2015 and August

2016, 2724 dementia-free community-dwellers aged 65+ with (at least) basic computer literacy and either two or more CVD risk factors or history of CVD or diabetes were enrolled in Finland, France, and the Netherlands. Eligibility was verified during an initial screening visit, and a baseline visit was conducted within the next two weeks. Potential participants were identified and recruited primarily through: (1) a population registry (Finland), (2) commercial mailing lists and a prevention centre (France), and (3) general practitioners (GPs) (Netherlands) (Supplemental Table 1). Intervention participants had access to an interactive platform and the remote support of a lifestyle coach; control participants were offered a simplified version of the platform, with no interactive features or coach support.
From April 2016 onwards, individuals scheduled for a HATICE screening visit (a priori eligible for the trial) were invited to complete the ACCEPT-HATICE questionnaire, preferably prior to screening, otherwise between the screening and baseline visits (Supplemental Table 1, Figure 1). Individuals who were ultimately not included in the HATICE trial, either due to ineligibility or withdrawal, were excluded from this analysis. A convenience sample of questionnaire respondents, who agreed to be re-contacted, were invited for a semi-structured interview within three months of their HATICE baseline visit. It was planned, given anticipated data saturation (due to the expected homogenous nature of study populations within each country), to perform approximately 15 interviews per country, and to maintain an equal balance between male/female and control/intervention group participants.
HATICE and ACCEPT-HATICE were approved by the local ethics committee in each country, and all participants provided written informed consent.

Data Collection

An online questionnaire exploring reasons for participating in the HATICE trial (Supplementary Material) was adapted from a questionnaire designed for a previous study.[139] Respondents were asked to what extent they agreed with a pre-defined list of statements relating to potential reasons for participating in the HATICE trial, and whether or not each statement was a reason why they agreed to participate. They could also specify other reasons, and were then asked which was their main reason for participating. Semi-structured interviews were carried out using a standard topic list (Supplementary Material) harmonised across the three countries, and covering an initial introduction of the interviewee, general perspectives on health and prevention, and reasons for participating in the HATICE trial. The topic list and recommendations for common procedures for conducting the interviews were based on previous experience and recent literature.[139] Interviewers were not aware of the questionnaire responses at the time of the interviews. All interviews were recorded and transcribed at verbatim in their original language.

Data analysis

Questionnaire respondents' baseline characteristics and reasons for participating were compared between countries using analysis of variance or Kruskal-Wallis tests for continuous variables, and chi squared or Fisher's exact tests for categorical variables. Analyses were performed with Stata version 14.1 (StataCorp LP, College Station, Texas).

Structured content analysis was applied to the qualitative interview data.[140] In each country, two independent researchers coded all interviews in the local language, using N.Vivo (version 11) or ATLAS.ti (version 1.6.0 (484)) software. The coding framework, initially based on the topic list, evolved inductively during regular meetings, held to ensure inter-coder consistency within- and across-countries, until it captured the core themes of the interviews. After local researchers reached consensus, core themes and selected quotes were translated into English. The formal content analysis was complemented by interpretive and iterative analyses designed to reveal the key trends of interviewee opinions in each country and identify between-country differences. Quantitative and qualitative results were then interpreted in parallel and main themes were aligned.

RESULTS

341 participants completed the questionnaire (191 in Finland, 103 in France, 47 in the Netherlands), and the overall response rate was 79% (Finland: 81%, France: 72%, Netherlands: 87%, p=0.039). Two thirds of the questionnaires were completed before the HATICE screening visit (Figure 1). The median age of respondents was 68.7 years, 48% were male, and 51% had university level education. Finnish respondents were younger than French and Dutch respondents, and had slightly poorer cognitive and physical performance, but were more physically active (Table 1).

15, 13, and 18 participants were interviewed in Finland, France and the Netherlands, respectively, on average 1.7 (range: 0.2-3.2) months after their HATICE baseline visit (Figure 1).

Most common reasons for participating in the HATICE trial

Figure 2 shows reasons for participation, based on the questionnaire results. Being interested in contributing to scientific progress (85% of all respondents), believing that improving diet and/or increasing level of physical exercise can have health benefits (84%), and the fact that participating would bring about additional medical monitoring (79%) were the three most common statements respondents agreed were reasons for participating in the trial. However, there were some between-country differences. Notably, significantly more questionnaire respondents in France (96%) and the Netherlands (94%) agreed that contributing to scientific progress was a reason for participation, compared to Finland (77%;

p<0.001), and Finnish (91%) and French (82%) respondents were more likely to agree that the potential health benefits of improving diet and/or increasing level of physical exercise were a reason for participating than Dutch respondents (62%; p<0.001) (Figure 2a).
Respondents also most frequently gave one of these three reasons as their main reason for participating in the HATICE trial, but while each one was cited by approximately a quarter of Finnish respondents, in France (51%) and the Netherlands (37%) "being interested in contributing to scientific progress" were the predominant main reason (Figure 2b).
These were also the most common reasons for participation evoked by interviewees. In-depth analysis of interview data is presented below to provide further insight into these reasons and cross-country differences.

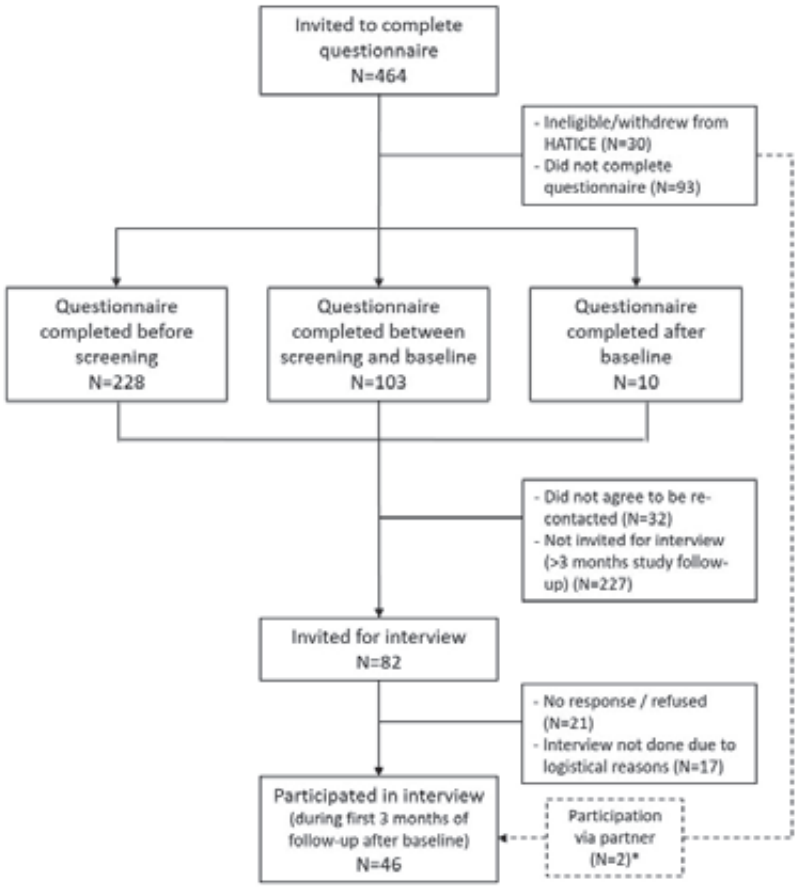

Figure 1 - Study flowchart

**Two interviewees did not complete the questionnaire, but participated in HATICE together with their partner, who completed the questionnaire and was invited for an interview.*

Table 1 - Characteristics of questionnaire respondents, by country

	Finland (N=191)	France (N=103)	Netherlands (N=47)	p
Recruitment method				
Invitation letter (pop. registry)	191 (100.0%)	-	-	N/A
Invitation letter (GP patients)	-	-	47 (100.0%)	
Invitation letter (mailing list)	-	10 (9.7%)	-	
Prevention centre	-	79 (76.7%)	-	
Other*	-	14 (13.6%)	-	
Socio-demographic characteristics				
Age	67.8 [66.5-69.8]	70.5 [67.3-74.0]	69.6 [66.9-74.9]	**<0.001**
Male	84 (44.0%)	58 (56.3%)	21 (44.7%)	0.117
University education	99 (51.8%)	56 (54.4%)	18 (38.3%)	0.170
Married/living with partner	155 (81.2%)	75 (72.8%)	32 (68.1%)	0.084
Cognition, mood and physical performance				
MMSE	28 [27-29]	29 [28-29]	29 [28-30]	**<0.001**
GDS	1 [0-3]	1 [1-4]	1 [1-2]	0.300
SPPB	11 [10-12]	12 [11-12]	12 [11-12]	**<0.001**
Cardiovascular risk profile				
Current smoker	14 (7.7%)	5 (5.1%)	1 (2.3%)	0.389
Obesity (BMI≥30)	75 (39.3%)	27 (26.2%)	18 (38.3%)	0.073
Hypertension	149 (78.0%)	75 (72.8%)	36 (76.6%)	0.606
Dyslipidaemia	182 (95.3%)	100 (97.1%)	47 (100.0%)	0.318
Diabetes mellitus	39 (20.4%)	13 (12.8%)	9 (19.2%)	0.257
<150 minutes of moderate intensity physical activity/week	30 (15.7%)	35 (34.0%)	11 (23.4%)	**0.002**
History of CVD**	35 (18.5%)	21 (20.8%)	10 (21.3%)	0.854

Data are presented as median [IQR] or N (%). Other recruitment strategies included: word of mouth, re-contacting participants of previous studies, and advertisements on institutional websites and in the press. Of the 13 French interviewees, 12 were recruited from the prevention centre, and the other from the mass mailing list invitation letter. ** At least one of the following: stroke/transient ischemic attack, myocardial infarction, angina pectoris, and/or peripheral arterial disease. BMI: body mass index; CVD: cardiovascular disease; GDS: Geriatric depression scale (score/15, higher score represents more depressive symptoms); MMSE: Mini Mental Status Examination (score/30, higher score represents better cognition); SPPB: Short Physical Performance Battery (score/12, higher score represents better physical performance).*

Contributing to science and altruism

Contribution to science and other altruistic reasons were frequently mentioned by interviewees in all countries as reasons to participate in the trial. Dutch and Finnish interviewees tended to talk about the usefulness of medical research in general terms, and the altruistic motives were discussed very broadly and/or in addition to other more important reasons, including personal benefits:

> *"What I just mentioned, I can learn things from that. And that can contribute to my health and, with the results from the complete trial, it can benefit society. That is my motive to participate." [NL-10]*

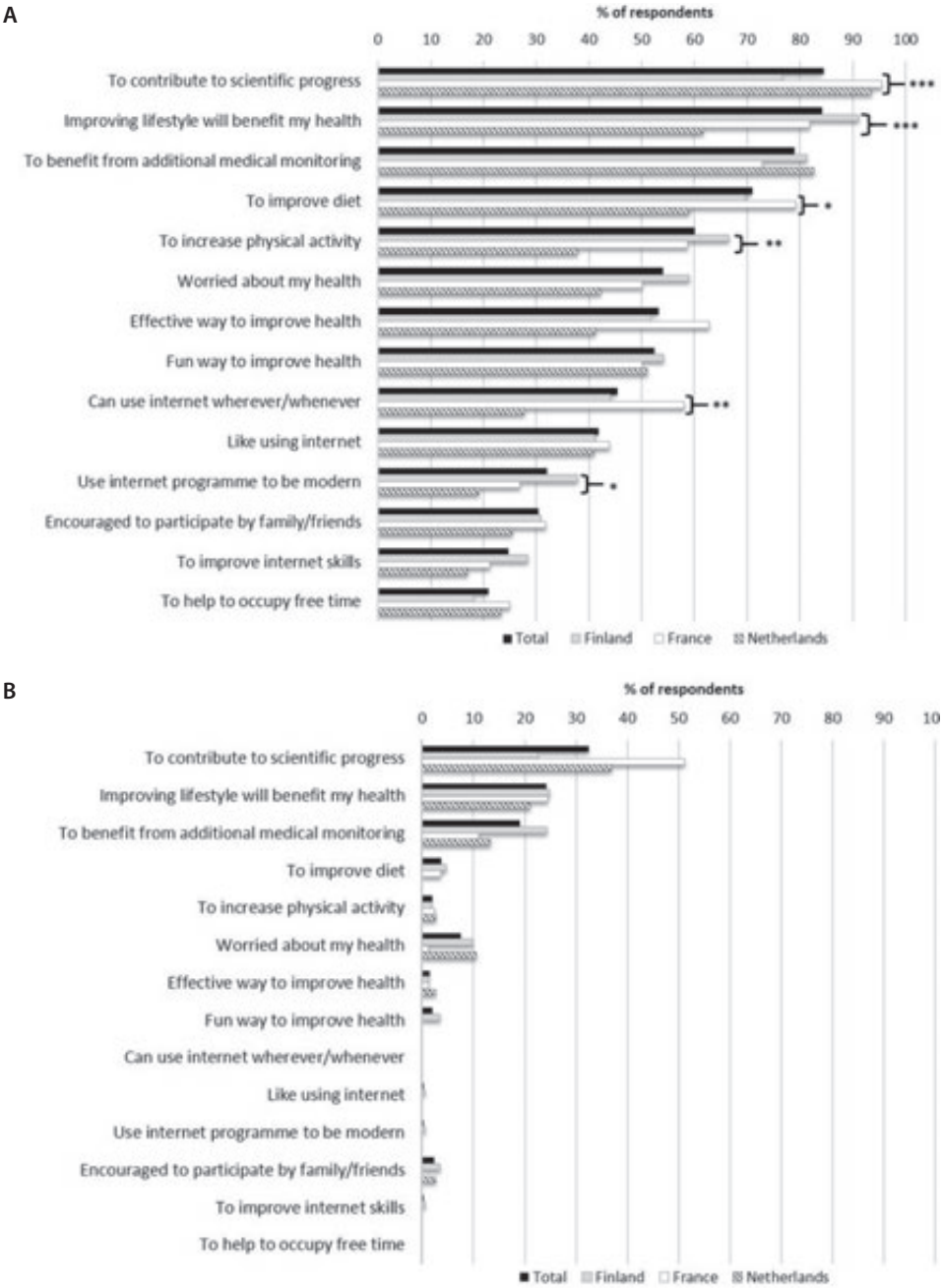

Figure 2 - Reasons for participation

A) Proportion of questionnaire respondents who agreed that this was a reason for participating in the HATICE trial

B) Proportion of questionnaire respondents who stated that this was their main reason for participating in the HATICE trial

*Asterisks indicate p-values for χ^2 tests (between-country comparison): *p<0.05; **p<0.01; ***p<0.001*

In Finland, many HATICE participants had previously taken part in studies and considered it a 'duty' to participate in medical research:

"Well I guess it [reason for participation] was dutifulness. When I was invited, I just thought 'why not'? Since I had no reason to refuse. I didn't think about it that much. I just wondered how many visits there would be, and if I have time to attend all of them, but… There weren't a lot of visits. I didn't really think about it very much. (…) It was an automatic decision." [FI-03]

French interviewees, however, gave specific meaning to their participation in a trial targeted towards healthy ageing, expecting it to contribute to a better understanding of healthy ageing and, thus, to improve the quality of life of the oldest old– a group to which they will soon belong to themselves. Ageing and being dependent on others evoked anxiety and fear, and many interviewees reported negative experiences concerning the care of older adults in institutions:

"Taking care of my mother is not easy. She is 89 and she is completely dependent. (…) We can't put her in a retirement home because she doesn't want us to, and so we have to take care of her ourselves. We are the last generation to do so. My daughters will not take care of me. They will not be able to; they will work until who knows when… We have already integrated the fact that for us, we will eventually end up in a retirement home. I am worried about ageing, and especially about being dependent. I see my completely dependent mother and I am projecting myself." [FR-06]

Such interviewees were particularly prone to raise 'contribution to science' as their main reason for participation in HATICE, and to admit that they would not necessarily commit to other kinds of studies:

"I want to help resolve the problem [of ageing] in general, and it also forces me to respect certain rules. And if it can be useful for someone else, why not? But I would say that, first and foremost, I am participating to advance medicine, just for that. (…) I don't really like the fact that I am being made to make changes, a new lifestyle, but perhaps it will also help me, bring me comfort in life and in my old age, and also be useful for others." [FR-08]

"My motivation to participate is as I said before: to see if this can help me and, through me, help others. (…) I volunteer in a nursing home and I tell myself that it's not very cool to grow old like this. And I hope, through physical and mental well-being, that we can find ways to protect ourselves and stay in good health as long as possible. Because when you get into a retirement home, it's not happy." [FR-02]

Improving lifestyle

Lifestyle improvement was also frequently mentioned as a reason for participation during interviews, and was expanded upon in particular by Dutch and Finnish interviewees. Some had a specific goal in mind, such as weight reduction, increasing physical activity, or improving dietary habits, or had already embarked on adopting a healthier lifestyle, and hoped that HATICE could provide external motivation and support:

"Interviewer: Do you have any wishes or goals for a healthy lifestyle?

Participant: To lose weight. (…) I wish I could do liposuction. Or for someone to guide me and push me to do things [physical activity]. I give up too easily. I think it [physical activity] is boring by myself and so I would prefer to do that with someone else or an organisation." [NL-09]

Lifestyle changes were generally perceived as useful and effective for the prevention of CVD in all three countries; however, the purpose of and motivation towards improved lifestyle did not seem to be preventing CVD as such, but to improve both current and future health and quality of life:

"Well of course it [motivation for prevention] is to feel more comfortable. I feel more comfortable physically when I'm lighter, and I presume that my ailments will be milder after I lose some weight." [FI-05]

Again, preventing functional dependence was a common concern:

"And I hope, through physical and mental well-being, that we can find ways to protect ourselves and stay in good health as long as possible. (...) I am not sure I will escape dependence, Alzheimer's disease and other pathologies. But if I can do my best to stay active as long as possible, then I should do it." [FR-02]

"Maybe it's the thought of not wanting to be a burden to others and that others don't need to take care of you. A strong constitution and condition and being healthy will help one feel more comfortable. (…) Some [CVD] diseases can be very mild, and they don't have much impact on daily life, but others can be quite serious. (…) That's the tricky thing: when you end up in a wheelchair or become dependent of others. With that in mind, one should aim to prevent that from happening." [FI-14]

Furthermore, some Dutch and Finnish interviewees hoped that lifestyle improvement would allow them to reduce or avoid medication:

"I am really curious to see if, as a consequence of my behavioural change due to the trial, the medication I use (…) maybe my blood thinners and cholesterol medication etcetera, that we can, well maybe not stop them, but see if I can handle a lower dosage." [NL-10]

"Well it made me worried [when the high blood pressure and cholesterol levels were discovered], but I was not scared. But I thought I needed to make changes now. (…) I did not really have any other options but to change my lifestyle. Or to start taking anti-hypertensives already in the mid-1990s. (…) And the diabetes drugs and so on. I rather changed my lifestyle so that I did not have to start taking those medications." [FI-04]

For some Dutch interviewees it felt like an obligation to themselves and/or their treating physicians to do everything in they could for a healthy lifestyle.

"You pay attention that you do enough physical exercise. I know all the risk factors. I don't have high blood pressure or those kind of things. But I don't eat a lot of salt. So I incorporate it in my life. And I think it would be an insult to those who have treated me if I didn't do that. A piece of gratitude also. And I think that is a sort of obligation that I feel." [NL-01]

Medical monitoring

Additional medical monitoring was an important reason for participating for Finnish and Dutch interviewees:

"Yes, I had hoped that they [from the HATICE trial] would conclude that I was very healthy (…), that there is nothing wrong with my arteries and heart." [NL-07]

It attracted not only proactive individuals already monitoring their health, but also those who were less worried about their health or tended to postpone or avoid seeking medical advice. For such individuals, participation provides a free and convenient opportunity to ascertain good health status:

"Well, [I decided to participate] just because I'm so lazy to book an appointment or see the doctor. I've already been in so many trials, I've always received the medical check-up there. Like for example my thyroid disease that was discovered in one of these studies, I probably wouldn't have seen a doctor otherwise. It is good to have regular follow-up and monitoring if something occurs. And it's free of charge. And all the appointments are booked for me and I don't need to… It is good that it's so easy (…) I'm too lazy to book any appointments. In this trial they do all the blood tests regularly and I know exactly where I stand. " [FI-13]

In the Netherlands, interviewees who appreciated medical monitoring often mentioned that they did not expect anything to be wrong; they merely felt comforted by the check-up. In Finland, interviewees considered medical monitoring in HATICE relevant because of difficulties accessing regular health care, particularly for prevention purposes, and notably after retirement when occupational health care services are no longer available:

"After retirement, there are no regular follow-ups anymore. One should seek medical attention himself, if needed. (…) And maybe [I decided to participate] also because I'm not in working life anymore. One doesn't go to the health care centre every year or even every other year to get the blood tests and other things done. Somehow it feels that they [healthcare professional] are so busy and it's impossible to reach them. Therefore, it just doesn't get done. I just mentioned earlier to you that the health care system works well, but actually, when you need the services, it's difficult to access. And then the fact that I'm not sick and I should explain them why I need the blood tests and why my values need to be monitored. I don't know if I've got the right impression, but sometimes it feels like they don't think it's necessary at all. A healthy person just wants to get tested for no reason. When I found out about this trial, I thought that, at least for 18 months, someone will examine me." [FI-07]

For some Finnish and Dutch interviewees, detection of CVD/memory disorders or their risk factors also motivated participation, particularly when there was a family history of such conditions:

"My father has both heart disease and a memory disorder. Of course, I'm interested in finding out what my situation is." [FI-09]

French interviewees did not spontaneously mention medical monitoring as a motive for

participation, but frequently mentioned having a close and trustworthy relationship with their own GP, and that regular health care was relatively easy to access.

Impact of Internet, and other reasons for participating in the HATICE trial

Overall, less than 5% of questionnaire respondents stated that an Internet-related factor was their main reason for participating (Figure 2b). The majority, however, agreed that using an Internet platform was a fun and/or effective way to improve health (Figure 2a). Other Internet-related factors influenced participation for less than 50% of respondents, and some between-country differences were observed (Figure 2a). Interviewees did not consider Internet-related factors a major influence on their decision to participate. However, contributing to developing an Internet health tool, and the convenience of having continuous access to an Internet intervention were mentioned by some:

"I said yes [to the stud] because, with Internet, it is not constraining. I can access the website anytime, even at night." [FR-09]

Interviewees with more extensive computer experience, in particular, thought that Internet could be a useful tool to improve lifestyle, and while the Internet in general was sometimes considered an unreliable source of information, the HATICE platform was considered trustworthy as it was offered by a university:

"Well, in this kind of a study, I think that… The premise is that it (the information) is reliable. (…) I have learned that information and knowledge generated at the university is reliable (…). (Interviewer: Right. So you trust the information you read in this study?) Yes. (Interviewer: What about information you read online?) Yes, well that should be viewed critically." [FI-05]

Potential barriers to participation associated with Internet use included lack of confidence in computer skills, although basic level of computer literacy was a prerequisite for HATICE participation:

"Well I thought for a second, will that work with the Internet? Just for a moment and the thought went away just as quickly, because it looked relatively easy. That was not too bad." [NL-07]

Also, the importance of social interaction and communication, even in an Internet-based intervention trial, was emphasised.

Several other reasons for participation emerged from the questionnaires and interviews, including being influenced by the invitation letter. A personalised letter, particularly for Dutch participants, when signed by their GP, conveyed a sense of reliability and trustworthiness:

(Interviewer: What was the reason you agreed to participate to HATICE, when you previously declined to participate in other studies?) "I think it was because of the way I was approached. It was just very clear and it was via my GP. Then I think, well that is probably very serious. That is not… someone can't do anything crazy with that or whatever. Reliable, that is what I mean." [NL-07]

Participants felt chosen and honoured to be asked to participate. Distance to the study centre and small number of study visits, occupying free time, getting a distraction during a stressful life period, and getting new information about CVD and memory disorders were also mentioned:

> *"Yes, they asked us and we felt honoured. I was very proud of it. Because I said to my son and brother-in-law, well we are participating in a study from the AMC [University Medical Centre]. He says, do you have to go there every time? I said, no, they come to my GP, so it is very close." [NL-04]*

Furthermore, participation was considered as fun, an opportunity to interact with people, and a way to satisfy curiosity. The non-pharmacological nature of the intervention attracted some participants.

DISCUSSION

In this cross-national, mixed-methods study, involving older European adults, altruistic reasons, wanting to improve one's lifestyle, and benefiting from additional medical monitoring were most frequent reasons for participating in an eHealth prevention trial. There were, however, some between-country variations in the level of importance given to each reason. Maintaining autonomy and preventing functional dependency, both for participants themselves, and for others, emerged as a key concern. The use of an Internet intervention did not seem to be a major motivator for participating in this trial.

As in previous studies,[135,137] wanting to support research and help others were frequent reasons for participating in the HATICE trial. However, contrary to Dutch and Finnish interviews, French interviews suggested that, rather than pure altruism (a concern for others in general), participation in this trial could be considered a fruit of social identification (a concern for a specific group, in this case older adults).[141] Traditional kinship relationships, attitudes and policies regarding the care of older adults vary across Europe,[142] ranging from the Nordic public service model to the Southern European family care model,[143] which may explain our findings. Furthermore, the French participants were recruited in South-West France, where the traditional family care model is currently shifting towards public service,[144,145] which may evoke fear about the changing and unfamiliar care patterns for this age-group, particularly given the negative experiences reported of old-age dependence and its management, especially in nursing homes.

Both questionnaire and interview responses highlighted that, particularly in Finland and the Netherlands, improving one's lifestyle was an important reason for participating, consistent with younger intervention trial participants' view,[146] but again, interviews revealed that the underlying motivation of lifestyle improvements in this age-group was to maintain functional independence. Independence in various aspects of life has previously been emphasised as an important issue for older adults.[147]

Consistent with previous studies,[148-150] our findings also indicated that personal health benefits and additional medical attention frequently motivate older adults to participate in a lifestyle-based prevention trial. However, in this multinational trial, the emphasis given to medical monitoring varied between countries. Finnish older adults in particular seemed to be motivated to participate for this reason, potentially because satisfaction with healthcare and perceived access to services has decreased in Finland over time,[151] and having unmet medical needs is more common than in other countries, including France and the Netherlands.[152] Some Finnish and Dutch interviewees felt discouraged from seeking health check-ups as part of routine medical care, unless there was something specifically wrong with them, but expressed a need to feel reassured that they were in good health. Although access to healthcare is not necessarily easier in France,[153] people perceive the quality of their care as relatively higher than in other European countries.[154] Furthermore, most French participants felt they already received sufficient care, and that HATICE was complementary to existing health services.

The main limitations of our study relate to selection bias. First, we used different recruitment methods in each country (e.g. many French participants were recruited through a prevention, while in the Netherlands, letters were sent to all potentially eligible patients in GP practices), which probably affected the between-country comparability of our samples. However, the different settings add diversity to our findings, and all participants nonetheless met the same eligibility criteria for the HATICE trial. Second, our participants are not representative of the entire older populations in the respective countries. Indeed, prevention trial participants tend to be healthier and more highly educated than the general population,[155] and selection bias could have been further increased in our study because, in order to be eligible, individuals had to have basic computer skills. This could also have influenced their views about participating in an Internet intervention. Finally, our sample was relatively small, and we only approached a convenience sample of HATICE participants, not all of whom agreed to participate in this sub-study, although response rates were high.

Nonetheless, to our knowledge, this is the first study examining older adults' reasons for participating in an eHealth prevention trial. Our work is strengthened by our mixed methods and cross-national approach, which highlighted the influence of differences in health, culture and social care systems. Additionally, our study was conducted during the recruitment phase of a real-life trial, rather than asking opinions about participating in a hypothetical trial, as in some previous studies.[137]

In addition to informing the design of recruitment strategies in future trials promoting healthy ageing, our results could also help to better tailor future intervention strategies

to the needs and desires of older adults, which in turn could improve recruitment. Box 1 presents our recommendations, based on our findings, some of which reinforce previous results relating to the HATICE trial.[156] This study focused on reasons for participation, and further research is required to identify potentially modifiable barriers to participation, and to study how reasons for participation affect retention, adherence or engagement.

Box 1 - Recommendations for designing recruitment strategies and interventions for future trials promoting healthy ageing in older adults

Recruitment

When inviting older adults to participate in future trials, recruitment could be facilitated by emphasising:

- Potential personal benefits, such as regular medical check-ups and contacts with healthcare professionals, particularly when access to them is difficult in the local public healthcare system. For some older adults this can facilitate the early detection of health problems, while for others it can provide reassurance that they are in good health. However, it should be underlined that participation in a trial does not and should not replace regular healthcare.
- Potential societal benefits, particularly those affecting older adults, such as preventing loss of autonomy.
- Influential study design features, including the involvement of respected local institutions or people (e.g. hospitals, universities or GPs); the logistical constraints (or lack thereof) of taking part (e.g. the number and location of study visits); and the expected ease of use of any technological devices required for the trial (which older adults may not be familiar or confident with, or mentioning that training will be provided to use such devices).

Intervention design

The following findings could be incorporated into the design of future interventions:

- Health information available on the internet can be perceived as unreliable by older adults, and so receiving understandable and accurate information from a reliable source, particularly regarding cardiovascular diseases and memory disorders/dementia, would be a benefit.
- Older people seem to require specific practical advice and encouragement about making lifestyle changes, particularly concerning diet and exercise, even if they are already motivated to do so.
- Having real-life (i.e. in person or by telephone) social interaction and communication are important elements to consider when designing interventions for older adults.
- Older adults may not feel confident about participating in an internet-based intervention, even if they have basic computer skills. Sufficient emphasis should therefore be given to training and ease of use for such interventions.

Supplemental Table 1 - Details of recruitment procedures for HATICE and ACCEPT-HATICE

		FINLAND	FRANCE	NETHERLANDS
Geographical area of the target population		- Kuopio: largest city in Eastern Finland (pop. approx. 117,000) - Joensuu: second largest city in Eastern Finland (pop. approx. 76,000)	- Toulouse (pop. approx. 440,000) and its surrounding areas, in the South-West of France	- Amsterdam (pop. approx. 820,000), capital city of the Netherlands, situated in the North of the country
HATICE Recruitment	**Channels**	Via a population registry	Via: (1) mass mailing campaigns (from commercially available mailing lists), (2) a pension fund prevention centre (CEDIP), (3) other methods (in occasional cases only), such as: word of mouth, re-contacting participants of previous studies, and advertisements on institutional websites and in the local press	Via GP practices
	Procedures	- Several rounds of mailing campaigns with an invitation letter signed by the University of Eastern Finland - Interested people contacted the research team by phone/email/ HATICE website - Potential participants were pre-screened by telephone - Screening & baseline visits were planned if eligible	(1) For individuals from the commercial mailing lists thought to be aged 65 and older: - Invitation letters were mailed from the local university hospital - Interested people contacted the research team by phone/email (2) Two recruitment methods were used at the CEDIP prevention centre: (i) A priori eligible individuals were identified during consultations and invited to take part in the study by the CEDIP staff; (ii) a self-completion postal questionnaire to verify the main eligibility criteria was sent to individuals aged ≥65 years who had attended a CEDIP prevention consultation since 2012 In all cases: - Potential participants were pre-screened by telephone - Screening & baseline visits were planned if eligible	- If GPs agreed to participate, they sent a letter to all of their patients aged>65 - Interested people contacted the research team via phone/ email/HATICE website - Potential participants were pre-screened by telephone - Screening & baseline visits were planned if eligible
ACCEPT-HATICE Recruitment	**Question-naires**	A priori eligible individuals at the pre-screening/screening phase of HATICE recruitment were invited by email to complete the questionnaire Some invitations were also sent between the HATICE screening and baseline visits, and occasionally shortly after the baseline visit		A priori eligible individuals were asked during the HATICE pre-screening phone call if they could be sent a questionnaire by email
	Interviews	As part of the questionnaire, respondents were asked if they agreed to be re-contacted. Those who responded positively could be approached for an interview		

ACCEPT-HATICE questionnaire

		I agree with this statement:				This is a reason why I accepted to participate in the HATICE study:	
		Totally agree	Somewhat agree	Somewhat disagree	Totally disagree	Yes	No
1.	I am interested in contributing to scientific progress	☐	☐	☐	☐	☐	☐
2.	My family and friends encouraged me to participate in the HATICE study	☐	☐	☐	☐	☐	☐
3.	Participating in the HATICE study will help me to occupy my free time	☐	☐	☐	☐	☐	☐
4.	Participating in the HATICE study will help me to improve my diet	☐	☐	☐	☐	☐	☐
5.	Participating in the HATICE study will help me to increase my level of physical exercise	☐	☐	☐	☐	☐	☐
6.	Participating in the HATICE study will enable me to receive specific medical monitoring	☐	☐	☐	☐	☐	☐
7.	Improving my diet and/or increasing my level of physical exercise can have benefits on my health	☐	☐	☐	☐	☐	☐
8.	I am worried about my health	☐	☐	☐	☐	☐	☐
9.	An internet-based programme is an effective way to improve my health	☐	☐	☐	☐	☐	☐
10.	An internet-based programme is a fun way to improve my health	☐	☐	☐	☐	☐	☐
11.	I like using the internet	☐	☐	☐	☐	☐	☐
12.	Participating in the HATICE study will help me to improve my internet skills	☐	☐	☐	☐	☐	☐
13.	Thanks to the internet, I can follow the programme when and where I want	☐	☐	☐	☐	☐	☐
14.	Participating in an internet-based programme is a way to show myself that I am modern (up-to-date)	☐	☐	☐	☐	☐	☐
	Please specify any other reasons you have for participating:						
15.		☐	☐	☐	☐	☐	☐
16.		☐	☐	☐	☐	☐	☐

Of all of these reasons, which is the **main reason** why you accepted to participate in the HATICE study? Please write in the box below the number (from the table above) corresponding to this reason:

The main reason why I accepted to participate in the HATICE study is the reason n° |__|__|

Would you agree to be re-contacted by a researcher to answer some further questions?

☐ YES ☐ NO

ACCEPT-HATICE interview guide

[Examples of potential questions are given in italics]

I. Reconstruction of life-course

Introduction: *First of all, I would like you to introduce yourself and to tell me about your daily activities.*

Sociodemographic data

- Marital status, number of children & grandchildren, family and friends, geographical proximity, retirement

Environmental and psychosocial factors related to health and quality of life

- Perceived and actual social support
- Social and cultural activities (leisure activities); Daily activities (domestic activities)
- Type of personality

Can you tell me a bit more about your family and friends? Can you tell me a bit more how you spend your time?

II. Relationship with health and perceived health status

Introduction: *I would like you to tell me about your health practices and how you react when you are faced with medical problems.*

Health practices: evaluation of the interviewees' behaviour when they have a health problem

- Relationship with doctors or medical/health professionals, frequency of consultations
- Relationship with medications (e.g. preference for prescribed or over the counter medications, or complementary medicine)

When you have a medical problem or a question about your health, what steps do you take? (E.g. in terms of consulting a doctor, or taking medication)

Perceived and actual health status

- Coping strategies for health problems

In general, how do you cope with health problems (for example, illness)? Do you tend to look for a solution? To ask for help or advice? Or do you generally tend to rely only on yourself? Do you tend to focus on a problem, or avoid it? Try to forget it?

- Causal attribution (origin and responsibility of illness) and locus of control

What do health and illness mean to you? What do you think about your health? Does it depend on you? On your doctors? On chance or destiny? Would you say that being ill is a punishment?

III. Perception of cardiovascular disease (CVD) risk and prevention

Introduction: *I would like you to tell me about cardiovascular disease: what it means to you and whether/how it can be prevented.*

Exploration of beliefs about CVD (e.g. origin/cause, quest of meaning)

Level of knowledge about risks, management, and consequences associated with CVD and risk factors

What do you know about cardiovascular disease and its management? What does it mean to you? What can one do to manage this disease or prevent it worsening?

Prevention practices for CVD and risk factors

What is your personal situation in terms of cardiovascular disease? Could you tell me what do you do to try to manage or prevent cardiovascular disease? And how do you find out what you should do? Do you look for information about health in general and about specific health problems that you may encounter?

Perceived utility and effectiveness of prevention of CVD via dietary habits, physical activity, medication
Role of Internet and online support in promoting healthy aging and preventing CVD

- Advantages and disadvantages of using Internet for health and prevention
- Level of credibility of information on the Internet
- Perceived effectiveness of prevention of CVD and potential risks

Could you tell me about how you use the internet (frequency, uses, on their own or with help, etc.)? What do you think about prevention on the internet? In what way do you think that internet can be a useful tool for your health?

V. Reasons for participation in the HATICE trial

Introduction: *Could you tell me about where you are up to in the HATICE trial, and why you decided to participate?*

ENGAGING OLDER PEOPLE IN AN INTERNET PLATFORM FOR CARDIOVASCULAR RISK SELF-MANAGEMENT

A QUALITATIVE STUDY AMONG DUTCH HATICE PARTICIPANTS

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ABSTRACT

Objectives To study older peoples' experiences with an interactive internet platform for cardiovascular self-management, to assess which factors influence initial and sustained engagement. To assess their views on future use within primary care.

Design Qualitative semistructured interview study, with thematic analysis.

Setting Primary care in the Netherlands.

Participants People ≥65 years with an increased risk of cardiovascular disease who used the 'Healthy Ageing Through Internet Counselling in the Elderly' (HATICE) internet platform with remote support of a coach. Participants were selected using a purposive sampling method based on gender, age, level of education, cardiovascular history, diabetes, duration of participation and login frequency.

Results We performed 17 interviews with 20 participants, including three couples. In the initial phase, platform engagement was influenced by perceived computer literacy of the participants, user-friendliness, acceptability and appropriateness of the intervention, and the initial interaction with the coach. Sustained platform use was mainly facilitated by a relationship of trust with the coach. Other facilitating factors were regular automatic and personal reminders, clear expectations of the platform, incorporation into daily routine, social support and a loyal and persistent attitude. Perceived lack of change in content of the platform could work both stimulating and discouraging. Participants supported the idea of embedding the platform into the primary care setting.

Conclusions Human support is crucial to initial and sustained engagement of older people in using an interactive internet platform for cardiovascular self-management. Regular reminders further facilitate sustained use, and increased tailoring to personal preference is recommended. Embedding the platform in primary health care may enhance future adoption.

INTRODUCTION

In view of global ageing and the associated increasing burden of cardiovascular disease (CVD), prevention has become crucial.[157] The effectiveness of preventive interventions is indisputable, even in old age.[158,159] However, adherence to long-term lifestyle and medication regimens remains a daunting challenge. Average adherence rates for chronic illnesses are as low as 50%.[160] Currently, in several countries, cardiovascular risk management programmes are implemented into primary care and delivered by practice nurses.[161] eHealth, that is, a method to deliver health services and information using the internet and related technologies, is a promising tool for delivery of prevention.[162] It can enable self-management and improve the reach and sustainability of pre-existing preventive programs.[163] In particular, an eHealth platform combined with human support (ie, a blended approach) has shown beneficial effects on cardiovascular risk factors.[138]

Previous research on eHealth interventions identified several important influential factors of engagement; personal motivation, incorporation into personal life and quality of the eHealth intervention.[164] However, it is unclear whether these are the same for initial and sustained engagement. For cardiovascular prevention, sustained engagement seems crucial, as the effectiveness of eHealth interventions on cardiovascular risk factors declines over time, especially after 1-year follow-up.[138] Also, an eHealth intervention specifically targeted at older people should have a specific age-friendly design.[165] It is important to assess the views of end users of an eHealth intervention to improve its chances of successful implementation.[166,167]

Our primary aim was to study older peoples' experiences with an interactive internet platform for cardiovascular self-management, to assess which factors influence initial and sustained engagement. Our secondary aim was to assess older people's views on implementation of such a platform in the primary care setting.

METHODS

Setting and participants

This qualitative study with semistructured interviews was performed among participants of the 'Healthy Ageing Through Internet Counselling in the Elderly' (HATICE, ISRCTN48151589) trial.[17] HATICE is designed to investigate whether an internet platform for cardiovascular self-management can improve the cardiovascular risk profile. People ≥65 years with an increased risk of CVD were recruited to participate in HATICE in the Netherlands, Finland and France. Computer illiteracy, defined as the inability to send an email, was an exclusion criteria for the trial. Through a thorough design and validation process, we developed the internet platform for cardiovascular self-management, adapted to meet the specific requirements of older people.[18,165] The intervention is based on Bandura's social-cognitive

theory for self-management and behaviour change and incorporated Michie's taxonomy for standardised definitions of behaviour change interventions.[168,169] The platform offers blended care by remote support of a health-coach trained in motivational interviewing techniques and the transtheoretical (or stages of change) model.[170,171] Participants can send messages and receive feedback from their coaches within the platform. Other functionalities of the platform include the ability to set lifestyle goals, record measurements (eg, blood pressure and weight), receive information on cardiovascular risk and healthy lifestyle and subscribe to lifestyle groups. The layout and navigation structure were kept simple to make the platform user-friendly for older people. The content was regularly updated with news items on relevant developments in cardiovascular prevention. The intervention was solely delivered via the platform, except for an initial inperson meeting with their coach at baseline, during which first lifestyle goals were set, and a phone call after 12 months follow-up.
This qualitative substudy was only performed among Dutch intervention participants. They were purposively sampled on gender, age, level of education, history of CVD, diabetes, duration of participation and login frequency. Participants who prematurely ended their participation were also invited. Twenty out of 32 participants who were invited by telephone were willing to partake in the interview. Main reasons for people to decline participation were lack of time and too little overall use of the platform, even though we specifically aimed to also include these participants. All participants provided written informed consent.

Data collection

Between July 2016 and January 2017 three researchers (TvM , CRLB and Suzanne van Rhijn) held semistructured interviews following an interview guide (online supplementeray appendix 1), focusing on participant experiences with the platform. We iteratively adapted the interview guide during the data collection period. For example, we decided to separately address initial and sustained use as distinct phases in the engagement and adoption of the intervention, as sustained engagement is especially challenging in lifestyle interventions.[138] During the interviews, participants were asked to log onto the platform to stimulate the discussion. The final part of the interview guide focused on the interaction with regular care, during which participants were asked if they preferred the platform to be incorporated in primary health care. The interviewers all had experience with conducting qualitative interviews. Two of the interviewers (TvM and CRLB) were involved in the design and maintenance of the platform (the participants were not made aware of this) and one (SvR) in the logistical support of the trial. The interviewers and participants had no professional relationship prior to the interview. Participants were interviewed in private at their homes, and the interviews lasted approximately 50 minutes. No repeat interviews were deemed necessary. Interviews were audiotaped and transcribed verbatim, and during the interviews, field notes were taken.

Coding and analysis

Two researchers (TvM and CRLB) thematically analysed the transcripts in an iterative process.[100] First, each researcher independently coded transcripts following an inductive approach; next, the researchers discussed each other's codes to achieve interobserver agreement. Subsequently, the researchers together categorized the codes to generate a structure of main themes and subthemes. Themes were derived from the data and were not hypothesized prior to data collection. At several points during the analysis process, results were discussed with other team members to ensure independent interpretation. After the first seven interviews, the interview guide was adapted based on one of these discussions, leading to a better distinction between initial and sustained engagement with the platform. Questions about initial engagement were asked to all participants and about sustained engagement to participants who had been in the study for at least 6 months. After 17 interviews, data saturation was reached as no new (sub)themes or issues emerged.

RESULTS

We performed 17 interviews with 20 participants (table 1). Three interviews took place with couples participating in the HATICE trial together, one of which had prematurely dropped out from the trial. The age of the participants ranged from 65 to 84 years. Ten (50%) participants had a history of CVD, and six (30%) had diabetes. Length of participation in the trial ranged from short (2-3 months, n=8 (40%)), intermediate (7-11 months, n=6 (30%)), to long (14-17 months, n=6 (30%)).

Table 1 - Characteristics of the participants

	Participant characteristics					Study characteristics		
Nr.	**Gender**	**Age**	**Education level***	**CVD**	**DM**	**FU duration (mo)**	**Partner partic. in HATICE**	**Login frequency (per mo)**
1	M	73	High	+	-	2.6	+	0.6
	F	66	Intermediate	-	-	2.6	+	0.5
2	F	67	Intermediate	+	+	2.2	-	3.2
3	F	84	Low	-	-	3.2	-	2.7
4	M	71	High	-	-	2.4	-	4.4
5	F	67	Intermediate	-	-	2.3	-	0.3
6	M	68	High	-	-	2.3	+	0.4
	F	70	Intermediate	-	-	2.3	+	0.7
7**	F	71	Intermediate	+	+	10.5	+	0.7
	M	74	Intermediate	-	-	10.3	+	0.9
8	M	65	Low	+	+	8.4	-	0.6

Table 1 - Continued

	Participant characteristics					Study characteristics		
Nr.	**Gender**	**Age**	**Education level***	**CVD**	**DM**	**FU duration (mo)**	**Partner partic. in HATICE**	**Login frequency (per mo)**
9	M	67	High	+	-	7.8	-	1.1
10	F	66	High	-	-	14.7	+	2.6
11	F	68	Intermediate	-	-	14.7	-	0.5
12	M	66	Low	+	+	7.1	-	1.8
13	F	74	High	-	-	9.4	-	4.7
14	M	65	Intermediate	+	+	15.8	-	0.8
15	M	67	Low	+	+	14.8	-	3.1
16	F	83	Intermediate	+	-	15.8	-	5.1
17	M	84	Low	+	-	16.6	-	3.2

*The characteristics are divided into participant characteristics and HATICE study characteristics. *Low education level indicates primary education or lower secondary education; intermediate, upper secondary education and postsecondary non-tertiary education; high, short-cycle tertiary education. ** Interview 7 was performed with participants that had recently (prematurely) ended their participation in HATICE. CVD, history of cardiovascular disease; DM, diabetes mellitus; F, female; FU, follow-up; HATICE, Healthy Ageing Through Internet Counselling in the Elderly; M, male; mo, month; partic, participating.*

The main themes and subthemes of factors that influence initial and sustained platform engagement are presented in table 2 and further explained in the text below.

Table 2- Themes and subthemes identified in the interviews of the facilitators (+) and barriers (-) in initial and sustained platform use

Initial platform use	**Sustained platform use**
User-friendliness for older people • Layout: simplicity, attractiveness (+/-) • Technical difficulties (-) • Perceived computer literacy (+/-)	Coach: long-term relationship of trust • Personal connection (+) • Content of messages (+/-) • Continuity of person (-)
Coach: the basis for a relationship of trust • Inperson baseline consultation (+) • Timing and content of messages (+)	Reactive use of the platform* (+)
Usefulness and perceived benefit of the intervention • Affinity with platform functionalities (including self-management) (+/-) • Awareness of cardiovascular risk (+/-) • Motivation for lifestyle change with increasing age (-)	Lifestyle change: expectations and experiences • Expectations of platform (+/-) • Benefits of lifestyle changes (+) • Setting a goal is burdensome (-) • Monitoring health (+)
	Incorporation into daily routine • Incorporation into daily routine (+/-) • Social (partner) support (+) • Continuity of care (+/-) • Time investment (+/-)
	Perceived lack of change in the platform (+/-)

**Reactive use indicates the preference of participants to use the platform in response to automatic or personal reminders.*

Initial platform engagement

User-friendliness for older people

Participants found the layout of the platform clear and simple which facilitated platform use. However, they stated that a more attractive platform could have encouraged them to log in more often:

> *"You should have a website that makes you think, when you have some spare time at night or in the afternoon, why don't I just have a look at HATICE." [P8]*

Technical difficulties in using the platform, for example, login difficulties, discouraged participants. Also, the notion of being inexperienced or incompetent with a computer or with the internet could hamper exploration of the platform and platform use. Sometimes, participants, together with their coach, found creative ways to use the platform when this was considered difficult:

> *"I'm not a computer freak. […] Once I receive a message then I answer it. And then she [coach] says, you should also complete it in the category that it belongs to [measurement]. To me it is not easy to find that […] But then later I notice that she has neatly entered it [in the measurement functionality]. I think that's fine." [P12]*

People who regarded themselves as inquisitive or eager to learn said this stimulated them in exploring the different functionalities of the platform.

Coach: the basis for a relationship of trust

For participants, trusting the coach was a prerequisite to talk about their health behaviours and potential lifestyle goals. The inperson baseline consultation with their coach was much appreciated, and formed a basis to build a relationship of trust. If the coach responded quickly and adequately to messages sent after the baseline visit, this stimulated platform engagement:

> *"At first I wanted… I really had no... I mean, I was actually curious. I did not think well this will… for me... At a certain moment, also because of her [coach], I immediately received a message back and she stimulated me, she said 'oh well done' and I don't know what more. That made me say, OK I will continue with this." [P12]*

Instead, if messages were not answered timely, participants became discouraged to continue using the platform. Some participants found personal contact through the messaging system insufficient to build a relationship and missed face-to-face or telephone contact.

Usefulness and perceived benefit of the intervention

During their first encounter with the platform, participants tended to focus on a small number of functionalities that appeared useful and relevant and continued with these over

time. This mostly concerned the messaging and measurement functionalities:

"When I receive an email I will go to the website and log in. And then I see what happened [message] and have a look. And sometimes I'm asked to complete a questionnaire and I do that. And other times, as is the case now, I'll go to the practice nurse; well then I have my blood and urine tested, and I send those along [send results to the coach]." [P16]

Some participants reported affinity with self-management and self-measuring of cardiovascular risk factors. They perceived the measurement functionality as useful and appropriate, facilitating platform use. Conversely, limited affinity with self-management could form a barrier to use this functionality:

"And I absolutely do not want my own blood pressure monitor. I did not want that when it [blood pressure] was too high and I certainly do not want it now that it is too low. Because I get very uh… It will influence me and I don't want that. I will not make myself crazy." [P3]

Participants who were aware of their cardiovascular risk status, in some cases because of a previous CVD, deemed the content of the platform relevant. Participants with limited perceived need to improve their lifestyle did not see how the platform could help them and tended to make limited use of it:

"I notice that it's about CVD. That is all fine, but I don't have that [history of CVD], so I will not engage any further with it [the platform]. [..] Indeed, if I do encounter it [CVD], than I would do it, but at this moment…" [P5]

Participants who already frequently visited their health care professional(s) stated they did not expect important additional benefit. Age also played a role as one of the oldest participants no longer prioritised adapting a healthier lifestyle because of his old age. Participants rarely adjusted or replaced the goals that were set at baseline. Limited use was made of the suggestions for lifestyle groups; participants expressed several reservations related to this functionality, such as that they thought that signing up created an obligation to participate and that groups would be dominated by older people with very limited functionalities.

Sustained platform engagement

Coach: long-term relationship of trust

As mentioned above, the coach was important to stimulate initial use of the platform. The coach also appeared pivotal in sustained platform use. If participants felt connected to the coach, participants felt inclined to keep using the platform and adhere to goals for lifestyle changes:

"Yes, because the coach makes you try to accomplish certain things. […] That would be more difficult without the coach. I don't know if… every time with the website… no, I don't think that that would work on its own [platform without coach]." [P9]

The message content was also important; a positive and personal tone could boost someone's motivation. One interviewee had experienced a change in coach during the trial. He stated this did not clearly change his platform use, although it did negatively impact his connection with the coach.

Reactive use of the platform

In many interviews, participants expressed difficulty to take initiative in using the platform, and found it easier to use the platform in a reactive way, for example, responding to automatic or personal reminders:

> *"Look, I like to participate in such a study, but… Perhaps I'm a bit more passive, that I think even if I have to have ten visits a year, that is fine. We will have a conversation; I will complete lists; that is all fine. But a website is… to figure things out, and to write things down, that is something… [Interviewer: Maybe you can call that initiative?] Yes I suppose that could be it." [P14]*

Participants who considered themselves as being loyal or persistent noted this stimulated sustained platform use:

> *"I was told to make contact once a month. And so I… It's stated here in my iPad: remember HATICE, report! And so we plan to do that." [P11]*

Lifestyle change: expectations and experiences

Being motivated for lifestyle change was a reason to continue using the platform and vice versa. This could be related to the reason to participate in the HATICE trial. Some participants were aware that the trial entailed active participation and hoped that they might benefit from it. Others, who participated to contribute to scientific progress, seemed to expect a more passive participation;that is, questionnaires or tests for which no self-initiative was required, and were not inclined to use the platform for self-management. Second, if people managed to reach their lifestyle goals and experienced its positive effects on their health, this stimulated sustained participation:

> *"Five kilometre laps. Yes, that is the minimum distance that I would like to walk each time. And I can achieve that quite nicely. And in that, I noticed that I started to feel fitter. That was really surprising. I always thought that I would stumble along through the rest of my life. And now I can... you get more fit. You have more enthusiasm to tackle things." [P14]*

In contrast, some participants felt setting a goal was an unpleasant burden. If they did not manage to reach their goal, they refrained from registering this on the platform or informing their coach, also, because they felt embarrassed or demotivated:

> *"You got sort of forced to... Because you had to make certain promises, like 'I will make sure to exercise so many times a day' and 'I will make sure I will lose weight'. Those kinds of things.*

Yes, that went against my gut feeling. […] You were sort of embarrassed if you said, well I actually did not do anything." [P7]

Participants appreciated the automatic feedback on entered measurements as it gave a reassuring feeling of having their health monitored. This facilitated regular logging in.

Incorporation into daily routines

Participants said that it was easier for them to keep using the platform if they had incorporated their platform use into their daily or weekly routine:

"Yes I like it. It works as a sort of support. In life you have all kinds of support systems, with your habits and your things, and this is one of them. It has become a part of… Yes well sometimes I can use it and sometimes I can't. But it has become a part of everything." [P2]

Disruption of daily routines, such as illnesses, negatively affected platform use. Social support, on the other hand, was an incentive for sustained use. This was especially true for couples participating in the HATICE trial together:

"I said, 'We should do something.' Then I started to fill those [questionnaires] in. And I said, 'Are you going to do that?' [Response partner:] 'Yes I will do that, but I am very busy.' I said, 'It will only take a minute.'" [P10]

Another important factor that facilitated platform-adherence was that the platform could improve the perceived continuity of support in self-management. In contrast to nurse-led periodic consultations, which are typical of secondary cardiovascular prevention programs, the platform felt like a source of continuous support that they could direct to any time:

"I already visit the practice nurse, but there is a lot of time in between [visits] and then yes… Of course together we assess the results, look at it and discuss it. But when I'm gone, it [the support] is also gone. Unless, of course, it turns out that I have to… that it's not quite OK. But then it's gone again. And this is, the continuity that you're always working on it, that is good." [P2]

Some participants found using the platform was time-consuming, which worked as a barrier. This could occur because of the misconception that they were obliged to regularly add measurements. In contrast, if participants felt the platform did not take too much of their time they were inclined to keep using it.

Perceived lack of change in the platform

Most participants were not aware of any changes made to the platform content, although others noted that news items were regularly updated. While several participants appreciated the stable content, others would have liked to see more changes over time, to stimulate their sustained engagement:

"Well I read that [information on cardiovascular risk] a little in the beginning and then that is that. Well now… And that does not change. I'm almost certain that this is the same as it was 1,5 year ago. […] So that is not inviting; to keep looking if there is something new." [P15]

The coach could influence this by varying the themes of conversation.

Future implementation

Participants indicated that the level of incorporation into the regular health care system was limited, and therefore, some of them felt the platform had no clear added value on top of the nurse-led cardiovascular risk management they already received within the primary health care. Regarding future implementation, participants felt positive toward incorporation of the platform into the existing primary care structure. Especially if the practice nurse were to become their coach, thus contributing to continuity of support, and if all measurements performed at home, and within primary and secondary care were integrated into the platform:

"The visit to the practice nurse is of course the real measurement. So I feel it's important to keep that, because it monitors your health, or at least a part of your health. That is important. But if all those measurements could be incorporated into this study, that would of course be very positive, because than you can compare it over several years or you can use it to look things up." [P9]

A concern of some of the participants was that this incorporation would lead to substitution of valued, inperson contacts with healthcare professionals by more anonymous exchange of messages via the platform. A participant suggested to add regular inperson visits with measurements to increase motivation, as a solution.

DISCUSSION

Summary

We have found that the support of a coach is crucial to initiate and sustain engagement of older people with an interactive internet platform for cardiovascular self-management. Factors associated with initial platform engagement are perceived computer literacy, usability and anticipated benefits of the platform, with special attention to the computer skills and preferences of older people. Factors associated with sustained platform engagement are regular automatic and personal reminders, clear expectations, incorporation into daily routine, and social support. Incorporation into primary healthcare could facilitate implementation of the platform and could improve the perceived continuity of support in self-management.

Strengths and limitations

The main strength of our study is that through our purposive sampling method we included both participants with a short, intermediate and long follow-up duration. This contributed to a clear distinction in motives for initial and sustained engagement. We used an iterative analysis method with multiple analysis rounds and adaptation of the interview guide throughout the process. Also, we followed the consolidated criteria for reporting qualitative research (COREQ) guidelines to facilitate reproducibility of study results.[102] A limitation of our study is that we only interviewed Dutch participants, potentially limiting the scope to the Dutch health care setting. Furthermore, the sample is prone to bias as our participants were willing to partake in both the HATICE trial and our qualitative substudy. This could have led to selection of people with a relative positive view on the intervention and with a high education level.[172] We minimised this potential bias by purposively sampling participants on education level and login frequency. Another possible source of bias is the fact that two of the interviewers and researchers analysing the data were involved in the development and maintenance of the platform. This could have influenced the intonation of questioning and interpretation of the data; however, their knowledge of the platform could also have stimulated the discussion. Independent analysis was ensured by incorporation of several analysis rounds with other team members.

Comparison with existing literature

Part of our results are in line with previous studies on engagement with eHealth interventions, such as on the influence of usability, perceived benefit and expectations of the intervention and the incorporation into personal life.[164] A new finding that is especially relevant for eHealth interventions on cardiovascular prevention is the crucial role of continuous support by a coach for sustained engagement. This has previously been described in a non-digital multi-domain preventive intervention.[148] In our study, the initial inperson contact was important to establish a relationship of trust between the participant and coach. For most people, maintenance of this relationship via a messaging system appeared to work well for a long-standing personal connection. The importance of this kind of blended care is emphasised by a meta-analysis showing a more pronounced effect on cardiovascular risk reduction.[138] Despite the use of motivational interviewing techniques and coaches following the transtheoretical model,[170,171] it was difficult to engage people with a low perceived benefit of the intervention. In general, motivational interviewing techniques delivered through eHealth have proven effective in inducing behavioural changes.[173] Nevertheless, a complete inperson approach might be preferable for participants in the precontemplation phase, when there is no intention to change behaviour, as even reading information about cardiovascular risk on the platform requires some level of initiative.[168]

A reactive approach, that is, responding to automatic and personal reminders, rather than a proactive approach seemed to suit most participants best. Previous studies have shown that electronic reminders are a useful tool to increase medication adherence.[174] However, it is uncertain whether this reactive approach sufficiently supports self-efficacy.[168] In line with the degrees of self-management proposed by Schermer this might be seen as compliant self-management.[175] Even though the interactive and flexible quality of the HATICE platform facilitates adoption of concordant self-management, that is, incorporation of the lifestyle advice into their personal life, this is not employed by everyone. Limited computer experience is an important barrier to platform use which may prohibit large-scale implementation. Increasing use of internet by older people is likely to overcome this limitation in the near future.[176]

A tailored platform

Our study shows that many aspects of multi-domain eHealth interventions rely heavily on personal preferences. The HATICE platform has been adjusted to the need for a personalised platform, by not imposing any obligations on which functionalities to use and giving participants the opportunity to tailor the frequency of automatic reminders to personal preferences. However, during the interviews, it appeared that people prefer an even more personalised platform. For instance, engagement was dependent on personal preference with regard to how much the content of the platform changes over time and the complexity of the platform changes, affinity with self-measurement, whether or not confrontation with lifestyle goals was appreciated, the ideal amount of time invested and the optimal frequency of reminders. As suggested by Bandura, it might be useful to tailor the platform content and the way it is provided based on a participants readiness to change.[168] This could, for example, be incorporated in a self-learning system that automatically tailors to personal characteristics, stages of change, needs and wishes.[177]

Implications for practice

During the HATICE trial, the platform was offered independently from regular care. Participants mentioned this separation as a barrier to platform use and agreed with the suggestion to incorporate it into the current primary care structure. Preventive eHealth interventions provide the opportunity to optimize continuity in support of self-management and reach individual targets with limited resources. In addition, implementation may improve sustained engagement with such an intervention.[178] Suggestions for this incorporation are to have the practice nurse work as coach, link measurements from electronic health records directly to the platform and align this with additional inperson visits for nurse-led cardiovascular risk management. Nevertheless, opportunities to implement the platform

probably differ based on the healthcare system. It is therefore crucial to properly evaluate the health care context and views of end users and healthcare professionals to support successful implementation.[167] Especially in healthcare systems with long distances or low resources, a preventive eHealth intervention may provide opportunities to improve existing preventive care.[179]

SUPPLEMENTARY MATERIAL

Interview guide

Opening question: *Could you tell me about your experiences with the HATICE platform?*

1. Use, experiences and opinion about the platform

General

Did you ever log onto the platform? What pages do you usually visit when you are logged on? What do you use the most and why? What don't you use and why? What do you think about the platform? Does the platform motivate you to change your lifestyle? Why?

Baseline

Why did you choose to participate in HATICE? Did your coach introduce you to the platform during the second visit? What did the coach mention about the platform? What was you first impression? What were you expectations of the platform? What was expected of you?

Initial phase

What were your first experiences with logging onto the platform? What parts of the platform did you use then? What appealed you to use the platform? And what repelled you to use the platform?

Adherence phase

How is that now? Do you use the platform differently now in comparison to the beginning? Why? Are there things that could have increased your use of the platform? If it would be possible, would you keep using the platform after the study ended? Why?

Coach

How do you experience the contact with your coach? What do you like? What don't you like? Do you feel that the coach is of added value to the platform? Would you prefer having telephone contact with your coach?

2. Interaction with regular care

Do you feel that the platform is of added value to regular care? To what extend? Have you consulted you general practitioner/practice nurse about the platform (or are you going to)? Why?
Would you like it if the general practitioner/practice nurse had insight into data from your personal platform? Why? If yes, what data would you like to share and what not?
(If applicable) Are there advantages or disadvantages to the platform in comparison to the care of your practice nurse?

EFFECT OF ANTIHYPERTENSIVE MEDICATION ON CEREBRAL SMALL VESSEL DISEASE

A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background and Purpose Hypertension is an important risk factor for cerebral small vessel disease (SVD). We aimed to study the effect of antihypertensive medication (AHM) on the progression and presence of cerebral SVD MRI markers.

Methods We performed a systematic literature search of MEDLINE, EMBASE, the Cochrane Library and BIOSIS up to January 30th 2017 for randomized controlled trials on the effect of AHM on ≥1 cerebral SVD MRI markers (i.e. white matter hyperintensities [WMH], lacunes, microbleeds, enlarged perivascular spaces, acute small subcortical infarcts, and brain atrophy) after ≥1 year. No restriction on study population was applied. The Cochrane Risk of Bias Tool was used to assess risk of bias and I^2 statistic for heterogeneity. We performed a random-effects meta-analysis using standardized mean difference (SMD) and meta-regression.

Results We included four trials with moderate-high level of evidence, including patients with stroke, with diabetes mellitus and persons ≥70 years of age. In the trials two MRI scans were performed with 28-47 months interval. Patients in the AHM group had less progression of WMH than controls (SMD -0.19; 95% CI -0.32 to -0.06; I^2=20%; n=1369) and a lower WMH volume at follow-up (SMD -0.15; 95% CI -0.39 to 0.08; I^2 67%; n=1177); although not reaching statistical significance. AHM had no effect on progression of brain atrophy (SMD -0.04; 95% CI -0.66 to 0.58; I^2=86%; n=406). None of the trials reported on other cerebral SVD markers. Larger systolic blood pressure difference at follow-up in the intervention versus control group was associated with less WMH progression (p-value=0.05).

Conclusions AHM has a protective effect on the progression of WMH, with a larger effect with increasing blood pressure lowering. We found no effect on brain atrophy. There are no trials on the effect of AHM on lacunes, microbleeds, enlarged perivascular spaces or acute small subcortical infarcts.

INTRODUCTION

Cerebral small vessel disease (SVD) is an aggregate term for damage to the small cerebral vessels of various aetiologies.[180] Neuroimaging correlates of SVD are white matter hyperintensities (WMH), lacunes, microbleeds, enlarged perivascular spaces, acute small subcortical infarcts, and brain atrophy.[181] With increasing severity it is related to cognitive impairment, gait problems, mood disturbances and urinary problems.[180] In addition, SVD is an important cause of spontaneous intracerebral hemorrhage.[182] Cerebral SVD has been proposed as a surrogate disease marker in clinical trials,[30] as it has a strong correlation with cognition, and its progress is measurable within a span of few years.[183]

Hypertension is an important risk factor for cerebral SVD.[184] The association is likely causal as hypertension can lead to damage to the vessel wall, thus leading to arteriolosclerosis and microaneurysms.[180] Although antihypertensive medication (AHM) is highly effective in preventing large artery cerebrovascular disease and is well implemented in clinical practice,[185] its effectiveness on SVD is yet unclear.

Our aim was to study the effect of antihypertensive medication on the progression and presence of MRI markers of cerebral SVD.

METHODS

Search strategy and study selection

The protocol of this systematic review and meta-analysis is registered on PROSPERO (CRD42017056873) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed.[36,37] We performed a systematic literature search up to January 30th 2017 in the databases MEDLINE, EMBASE, the Cochrane Library and BIOSIS. The search contained terms relating to AHM and cerebral SVD, including each individual SVD marker (Supplemental methods I, the complete search strategy). We reviewed the reference list of all selected articles for additional relevant studies.

Two reviewers (TvM and TA) screened all articles independent of one another and selected the appropriate articles, first based on title and abstract and then based on full text. Disagreement over eligibility was resolved through discussion between the reviewers. A third reviewer (FS) was available for final judgement if disagreements persisted. We included studies if they were (1) an RCT, (2) included an intervention with AHM which lasted for at least one year, (3) reported on progression during, or prevalence at, follow-up of at least one marker of cerebral SVD on MRI. SVD markers of interest were WMH, lacunes, microbleeds, enlarged perivascular spaces, acute small subcortical infarcts, and brain atrophy.[181] We included both placebo controlled RCTs and RCTs with other control conditions. We did not apply language restrictions nor restrictions on study population.

Data extraction

Two reviewers (TvM and TA) extracted the data and assessed the risk of bias independently. Discrepancies were resolved through discussion. We used a standardized, pre-piloted data extraction form to extract data on study characteristics, baseline characteristics, content of the intervention and control condition, MRI characteristics, outcomes of the different cerebral SVD markers, and funding sources. Risk of bias was assessed following the Cochrane Risk of Bias Tool and the overall quality with the *Grading of Recommendations, Assessment, Development and Evaluations* (GRADE) system.[38,39] We contacted the authors of the included trials in case data necessary for the meta-analysis were not available in the published results.

Statistical analysis

We pooled the individual cerebral SVD markers with a DerSimonian-Laird random-effects model. For the analyses on progression we used the difference between the baseline and follow-up MRI. For continuous outcomes we used a standardized mean difference (SMD) according to Hedges' g effect size,[38] because the included trials used different methods to measure and report on SVD. The SMD is calculated as the difference between the intervention and control group divided by the standard deviation (SD).[40] We assessed statistical heterogeneity between the included studies using the I^2 statistic.[186] With a funnel plot we visually assessed risk of publication bias. We transformed logarithmic values before they were entered in the meta-analysis (Supplemental methods II, additional information on the logarithmic transformation).[187] One of the included trials did not report on total WMH volume, but reported on WMH volume in the subcortical region and WMH classification in the periventricular region separately.[188] As the results on subcortical WMH were the only volumetric measurement, we included these in our meta-analysis. With pre-specified meta-regression analyses, we assessed the influence of difference in mean systolic blood pressure (SBP) at follow-up between the intervention and control group, mean reduction of SBP during follow-up in the intervention group, mean duration of the intervention, and mean age at baseline. We used R studio package meta for the statistical analyses and plots.[130]

RESULTS

The literature search resulted in 2595 individual articles (Figure 1). 27 articles were screened based on their full text and we included five articles in the qualitative and quantitative analyses reporting on four individual trials. Assessment of risk of bias in the included studies was low or unclear (Supplemental table I). The *Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes* (ACCORD-MIND) trial had a high risk of performance bias as treatment allocation was not blinded to participants or treating physicians due to the study

design comparing a target SBP of <120 mmHg to <140 mmHg.[189] The outcome assessment of the ACCORD-MIND trial was blinded. We assessed the meta-analyses on progression of WMH and WMH volume at follow-up as high level of evidence and on progression of brain atrophy as moderate level of evidence due to risk of publication bias (Supplemental figure I). Authors from the *Prevention Regimen for Effectively Avoiding Second Strokes* (PRoFESS) and *Study on Cognition and Prognosis in the Elderly* (SCOPE) trial supplied additional data for the meta-analysis.[188,190]

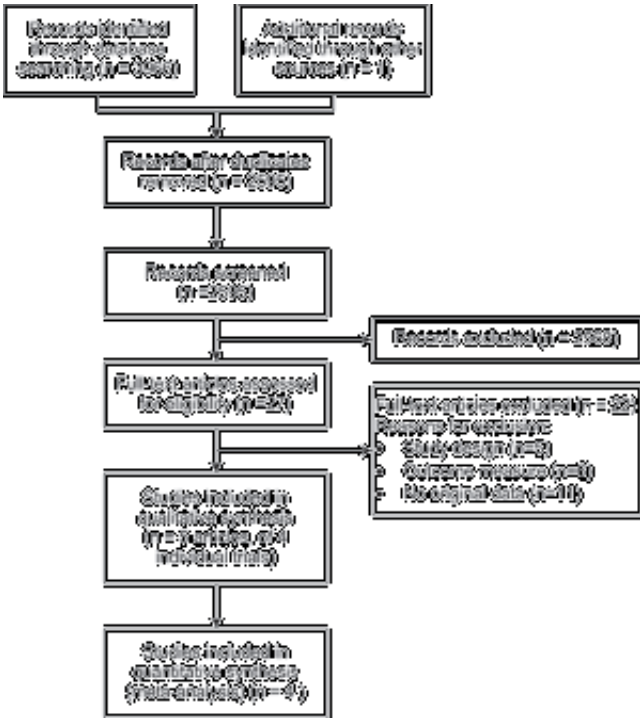


Figure 1 - Flowchart of study selection

The four trials included 1369 participants with available data at follow-up. Average follow-up ranged from 28-47 months (Table 1). Only the ACCORD-MIND trial was not placebo controlled. The ACCORD-MIND trial included patients with diabetes mellitus and an increased cardiovascular risk,[189] the PRoFESS and *Perindopril Protection Against Recurrent Stroke Study* (PROGRESS) trial stroke patients,[188,191] and the SCOPE trial individuals aged 70-89 years old.[190] Compared to the three other trials, participants from the SCOPE trial were substantially older and had a higher SBP at baseline. In the intervention groups mean SBP was decreased by 20 mmHg in the ACCORD-MIND trial, 11 mmHg in the PRoFESS trial, 13 mmHg in the PROGRESS trial and 26 mmHg in the SCOPE trial.

Cerebral SVD was a secondary outcome measure in all included trials. All four trials reported on WMH and two trials on brain atrophy (Table 2) as measured by automatic or manual measurement (Supplemental table II). The ACCORD-MIND trial published their results on WMH volume at final visit during the trial in a second paper which also included measurements after extended follow-up.[192] In the PRoFESS trial WMH progression and presence was reported as increase in subcortical WMH diameter. In the PROGRESS trial the progression of WMH volume consisted of the volume of new WMH lesions during follow-up and did not include the expansion of WMH lesions present at baseline. The SCOPE trial reported WMH volume as percentage of total brain volume (TBV). Brain atrophy was reported as volumetric measurement in the ACCORD-MIND trial and as percentage of TBV in the SCOPE trial. None of the trials reported on lacunes, microbleeds, enlarged perivascular spaces or acute small subcortical infarcts.

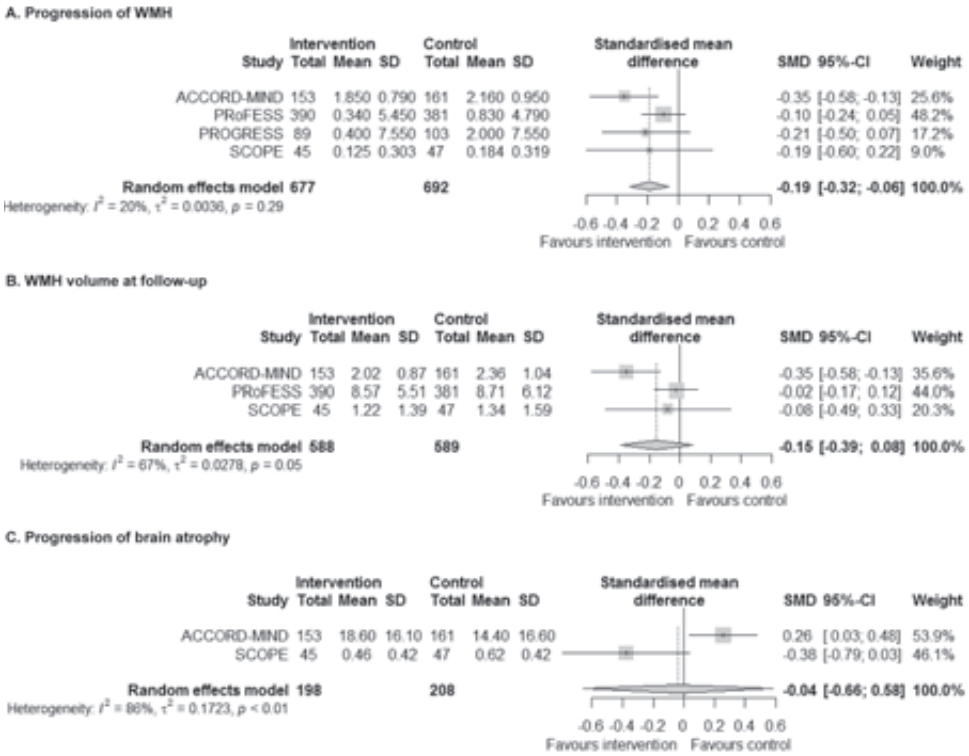


Figure 2 - Forest plot on the effect of AHM on WMH and atrophy
SD indicates standard deviation; SMD, standardised mean difference; CI, confidence interval.

Table 1 - Study characteristics

	ACCORD-MIND	PRoFESS	PROGRESS	SCOPE
Year of publication	2014	2012	2005	2007
Funding	National Institute of Aging and the National Heart, Lung, and Blood Institute of the National Institutes of Health	Boehringer Ingelheim	Servier, the Health Research Council of New Zealand and the National Health and Medical Research Council of Australia	AstraZeneca International and Astra Research Foundation UK
Continent	North America	North and South America, Australia, Asia, Europe	Europe	Europe, North America, Asia
Study design	2x2 factorial*	2x2 factorial†	Parallel-group	Parallel-group
Intervention	Intensive BP control (SBP <120 mmHg)	Telmisartan 80mg	Perindopril 4 mg and indapamide 2.5 mg	Candesartan 8mg
Control	Standard BP control (SBP <140 mmHg)	Placebo	Placebo	Placebo
Inclusion criteria	DM2, a high risk for cardiovascular events (prevalent CVD or additional cardiovascular risk factors) and a SBP 130-180 mmHg	An ischemic stroke in the previous 90 days, ≥55 years‡ and a SBP <180 mmHg and DBP <110 mmHg	TIA or an ischemic or hemorrhagic stroke (excl. SAH) in the previous 5 years	People aged 70-89 years with a SBP 160-190 mmHg and/or a DBP 90-99 mmHg†
Duration FU (mnt)	Mean 40 (SD n.r)	27.9 (SD 7.6)	Median 36 (range 24-49)	47.3 (SD 0.2)
Number of participants	314	771	192	92
Age (years)	61.7 (SD 4.9)§	65.5 (SD 8.1)§	60.9 (SD 12.1)	77 (SD 4)
Sex (male)	184 (59%)	496 (64%)	146 (76%)	42 (46%)
SBP, intervention				
· **Baseline**	138.7 (SD 17.5)	146.0 (SD 16.3)	144.3 (SD 20)	167 (SD 8)°
· **Follow-up**	119.0 (SD 12.0)	134.9 (SD 20.5)	131.8 (SD n.r.)	141 (SD 11)
· **Change**	-19.7	-11.1	-12.5	-26
SBP, control				
· **Baseline**	139.3 (SD 16.9)	145.5 (SD 16.3)	142.2 (SD 19.7)	167 (SD 8)‖
· **Follow-up**	133.2 (SD 14.6)	137.4 (SD 18.2)	140.9 (SD n.r.)	147 (SD 12)
· **Change**	-6.1	-8.1	-1.3	-20

*Data are presented as number (percentage) or mean (standard deviation), unless it is stated otherwise. Change in systolic blood pressure indicates the change between baseline and follow-up. *The additional intervention in the ACCORD-MIND trial included intensive glycaemia control. †In the SCOPE trial use of antihypertensive medication other than hydrochlorothiazide or recent (<6 months) stroke or myocardial infarction were exclusion criteria (among others). †Additional interventions in the PRoFESS trial included dipyridamole plus aspirin or clopidogrel. ‡ In the PRoFESS trial patients aged 50-54 years could also be included if they had a stroke and ≥2 cardiovascular risk factors. § When no data on the entire study population was given, the summary statistic of the intervention group was presented. ‖ When no separate data on the intervention and control group was given, the summary statistic of the entire study population was given. UK indicates united kingdom; FU, follow-up; mnt, months; BP, blood pressure; SBP, systolic blood pressure; TIA, transient ischemic attack; SAH, subarachnoid hemorrhage; DBP, diastolic blood pressure; DM2, diabetes mellitus type 2; CVD, cardiovascular disease; n.r. not reported.*

Table 2 - Results on cerebral small vessel disease

Outcome		Trial	Unit	Baseline		Follow-up		Change between baseline and follow-up	
				Interv.	Control	Interv.	Control	Interv.	Control
WMH	**Total WMH**	ACCORD-MIND	cm^3 (log transf.)	0.09	0.09	0.62 (95% CI 0.55-0.68)*	0.77 (95% CI 0.71-0.84)*	0.53 (95% CI 0.46-0.59)*	0.68 (95% CI 0.62-0.75)*
		PROGRESS	mm^3	n.r.	n.r.	n.r.	n.r.	0.4 (SE 0.8)†	2.0 (SE 0.7)†
		SCOPE	% of TBV	1.09 (SD 1.23)	1.16 (SD 1.39)	1.22 (SD 1.39)	1.34 (SD 1.59)	0.13 (SD 0.30)	0.18 (SD 0.32)
	Sub-cortical WMH	PRoFESS	mm	8.17 (SD 6.19)	7.81 (SD 5.86)	8.57 (SD 5.51)	8.71 (SD 6.12)	0.34 (SD 5.45)	0.83 (SD 4.79)
		SCOPE	% of TBV	0.35 (SD 0.72)	0.29 (SD 0.45)	0.39 (SD 0.76)	0.36 (SD 0.56) 1.23	0.03 (SD 0.13)	0.07 (SD 0.14)
	Peri-ventricular WMH	PRoFESS	score	2.92 (SD 2.31)	2.87 (SD 2.29)	3.48 (SD 2.55)	3.3 (SD 2.46)	0.54 (SD 1.89)	0.40 (SD 1.86)
Brain atrophy	**TBV**	ACCORD-MIND	cm^3	921.5 (SD n.r.)	921.5 (SD n.r.)	900.7 (SD 96.9)	904.9 (SD 98.7)	-18.6 (SD 16.1)	-14.4 (SD 16.6)
	Brain atrophy	SCOPE	% of TBV	n.r.	n.r.	n.r.	n.r.	0.46 (SD 0.42)	0.62 (SD 0.42)
Lacunes		None							
Microbleeds		None							
Enlarged perivascular spaces		None							
Acute small subcortical infarcts		None							

*Data is presented as mean plus a measure of variance (standard deviation, standard error or 95% confidence interval). *ACCORD-MIND data on WMH is adjusted for baseline outcome measure, visit, and randomized group allocation; Clinical Centre Network; and history of cardiovascular disease. †The progression of WMH in PROGRESS is only the volume of new WMH lesions. Interv. indicates intervention; WMH, white matter hyperintensities; TBV, total brain volume; CI, confidence interval.*

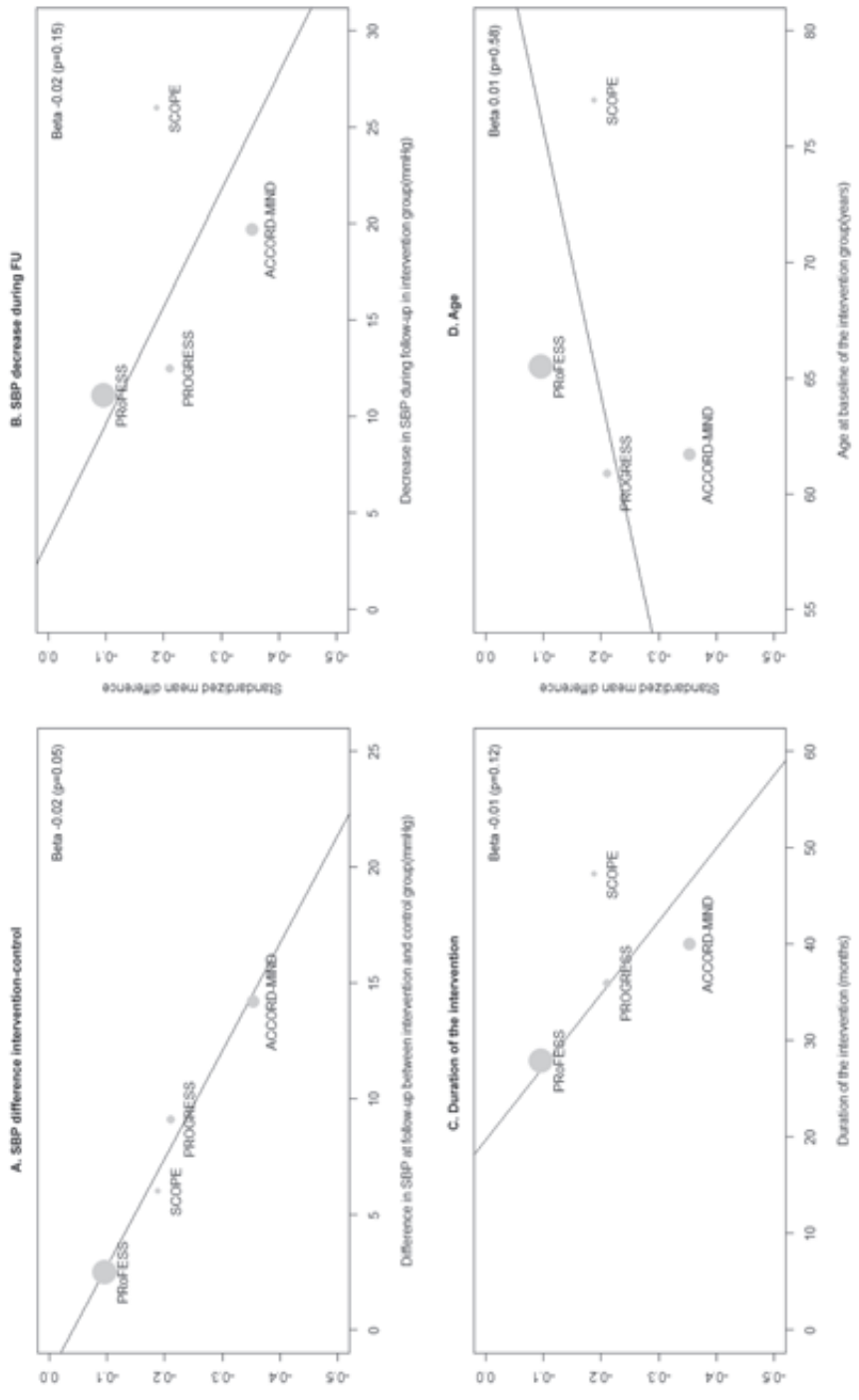


Figure 3 - Meta-regression on the influence of blood pressure, intervention duration and age on WMH progression

WMH indicates white matter hyperintensities; SBP, systolic blood pressure; FU, follow-up

All four studies (n=1369) reported progression of WMH, with a pooled SMD of -0.19 (95% CI -0.32 to -0.06; I^2 20%; Figure 2A). WMH volume at follow-up was reported in three studies (n=1177), with a SMD between the intervention and control groups of -0.15 (95% confidence interval [CI] -0.39 to 0.08; I^2 67%; Figure 2B). The SMD for progression of brain atrophy based on two studies (n=406) was -0.04 (95% CI -0.66 to 0.58; I^2 86%; Figure 2C). One trial reported on presence of brain atrophy at follow-up, with a significant lower total brain volume in the intervention versus the control group (Table 2).

Trials with a larger contrast in systolic BP between the treatment groups seemed to have larger effects on WMH progression (beta -0.02; p-value=0.05; Figure 3A). There was no association between progression of WMH and decrease in SBP during follow-up in the intervention group (beta -0.02; p-value=0.15), duration of the intervention (beta -0.01; p-value=0.12) or age (beta 0.01; p-value=0.58) (Figure 3B-D). We found comparable results for the meta-regression analyses on WMH volume at follow-up (Supplemental figure II).

DISCUSSION

We found that AHM is effective in slowing the progression of WMH. The preventive effect on progression of WMH is based on four trials with high quality of evidence, low statistical heterogeneity and diverse study populations with both patients with stroke, with diabetes and older individuals. The effect on progression of WMH is strongest in trials with a higher difference in SBP at follow-up between the intervention and control group and is, within the studied populations, independent of age. AHM is not effective in slowing the progression of brain atrophy, but the number of studies assessing progression of atrophy was limited and results were heterogeneous. None of the trials assessed the effect of AHM on lacunes, microbleeds, enlarged perivascular spaces or acute small subcortical infarcts.

The preventive effect of AHM on progression of WMH is in line with our hypothesis. Our finding that AHM had a non-significant effect on WMH volume at follow-up is probably due to a lack of statistical power, because the meta-analysis on WMH volume at follow-up included one trial less than the analysis on progression. Another explanation for the discrepancy in significance may be a modest difference in WMH volume at baseline in favor of the control group in the PRoFESS trial that had the largest number of participants. The point-estimate for the two analyses was in the same direction supporting our hypothesis that AHM can slow down progression of AMH. The heterogeneous results we found on brain atrophy are not in line with our hypothesis. A possible explanation for this is that brain atrophy is modulated by several other pathologic mechanisms besides SVD, including neurodegeneration, on which AHM may have limited effect.[193] Another explanation might be that a target SBP of <120 mmHg was too low in the ACCORD-MIND study population with diabetes and an increased cardiovascular risk. The increased cardiovascular burden

may have already impaired the cerebral autoregulation before the start of the trial.[194] A low blood pressure (BP), especially a low diastolic BP (63.3 mmHg at follow-up in the ACCORD-MIND intervention group), may then cause inadequate cerebral perfusion, which may contribute to neurodegeneration.[194,195]

For the relation of BP with mortality, cardiovascular events and potentially also dementia, there appears to be a 'J-shaped curve', indicating that both low and high BP levels are associated with an increased risk of disease or death.[117,196,197] Such a J-shaped association with BP has also been suggested for the development of WMH.[198] However, the ACCORD-MIND trial had a target SBP of <120 mmHg in the intervention group and showed the strongest effect on curtailing progression of WMH.[189] Our meta-analysis is therefore suggestive for a linear and not a J-shaped association, although meta-regression with only 4 RCTs has to be interpreted with caution. It will be interesting to see if the recently completed, but not yet published, *Systolic Blood Pressure Intervention Trial memory and cognition in decreased hypertension* (SPRINT-MIND),[199] which assessed the effect of a target SBP <120 mmHg in a population with an increased cardiovascular risk but without diabetes, will show comparable beneficial results on WMH and perhaps also other SVD markers.

A recently published study has shown that progression of WMH is not linear over time.[200] Instead, WMH tends to progress faster in people with a higher WMH load at baseline, compared to people with a lower WMH load. From a prevention perspective the ideal timing of AHM for the prevention of WMH seems to be early in the course of hypertension. This would be another argument for early treatment of hypertension in the ongoing discussion whether or not to start AHM in people with hypertension but a low overall cardiovascular risk.[201] However, with slow progression rates of WMH in the early stages it may be difficult to prove the effectiveness of AHM within a reasonable timeframe. This is less of an issue in later stages of WMH progression (i.e. in older people or people with an increased cardiovascular risk) as more contrast in WMH volume in comparison with controls may be achieved.[202] Subgroup analysis of the PROGRESS trial showed a stronger effect of AHM in participants with severe WMH at baseline, supporting this last hypothesis.[191] Whether an intervention in participants with severe WMH load leads to clinical benefit on cognition or gait is unclear.

SVD has been suggested as surrogate outcome in trials to prevent dementia.[30] In our meta-analysis we have shown that AHM can slow the progression of WMH. We did not assess the predictive value of this effect on the prevention of dementia or other clinical adverse outcomes. In the observational extension study of the ACCORD-MIND trial no long-term effect on cognition was observed.[192] Whether this was caused by the diminished effect of the intervention on BP during the observational extension period (SBP increased to ±130 mmHg in the intervention group), selective drop-out of those with the worst cognitive function or the absence of a clinical effect is unclear.

As far as we are aware, this is the first systematic review and meta-analysis assessing the

effect of AHM on cerebral SVD. Our thorough literature search and systematic selection process gives a clear overview of the level of evidence available and the knowledge gaps for which further research is required. There is no evidence on the effect of AHM on lacunes, microbleeds, enlarged perivascular spaces and acute small subcortical infarcts and also the effect on brain atrophy requires further study. Ultimately, an answer is needed on the question whether AHM leads to a lower risk of important clinical outcomes, including dementia and mobility. A limitation of our review is the heterogeneity of methods used to quantify cerebral SVD. In our meta-analysis we accounted for the heterogeneity by using a random-effects model and a standardized outcome measure. Generalizability of SVD trials may be improved if current and future researchers adhere to the definitions and methodological guidelines for the measurement of SVD that have been published previously.[181,203] Unfortunately, due to the limited number of studies included, no subgroup analyses based on characteristics of the different study populations were possible.

CONCLUSIONS

To conclude, antihypertensive medication can limit the progression of white matter hyperintensities. It is not effective in slowing down the progression of brain atrophy, although results are heterogeneous and based on a small sample. No evidence is available on the effect of AHM on lacunes, microbleeds, enlarged perivascular spaces or acute small subcortical infarcts. The effect of AHM on the progression of WMH supports the hypothesis of a causal pathway between hypertension and WMH. As the effect is stronger in studies with a lower SBP at follow-up in the intervention versus the control group, a low target SBP appears most appropriate to prevent the progression of WMH. Whether the preventive effect on WMH also leads to prevention of cognitive decline or deterioration of gait is unclear. It is therefore uncertain whether WMH is an appropriate surrogate outcome for clinical trials. The effectivity of AHM on the progression of WMH over the course of several years underscores the potential of intervening in the continuing process of damage to the cerebrovasculature, preventing brain damage and ultimately preventing dementia.

SUPPLEMENTARY MATERIAL

Supplemental methods I. Search strategy

Medline	
1	(((“Lacunar stroke*” or “small vessel disease” or “Cerebral Microangiopath*” or “subcortical infarct*” or “White matter hyperintens*” or “Cerebral microbleed*” or “Brain atroph*” or “Small vessel cerebrovascular diseas*” or “Small vessel cerebrovascular disorder*” or SVD or “lacunar infarct*” or “silent brain infarct*” or “subcortical stroke*” or “subcortical cystic infarct*” or “cerebral lacunar lesion*” or “deep lacunar lesion*” or “subcortical lacunar lesion*” or “symptomatic lacunar lesion*” or “a symptomatic lacunar lesion*” or “Small vessel disease stroke” or “small deep infarct*” or “perforator territory infarct*” or “lacunar arteriopathy” or “white matter lesion*” or WML or “white matter hyperintensities” or WMH or leukoaraiosis or leucoaraiosis or “Virchow-Robin space*” or “etat crible” or “type 3 lacune*” or “white matter change*” or “WMC” or “changes in white matter” or “leukoencephalopathy” or “white matter disease” or “WMD” or “white matter damage” or (“perivascular space*” and (cerebr* or brain)) or (lacune* and (cerebr* or brain)) or (“deep infarct*” and (cerebr* or brain)) or (“deep stroke*” and (cerebr* or brain)) or microinfarct*) and (cerebr* or brain)) or “brain microbleed” or “chronic microbleed” or “silent microbleed” or “asymptomatic microbleed” or “cerebral microhemorrhage” or “cerebral microhaemorrhage” or “dot-like hemosiderin spot*” or “dot-like hemosiderin deposition” or “small vessel infarct*” or “small vessel stroke*” or “microscopic infarct*” or “brain volum*” or “cerebral volum*”).ti,ab,kf.
2	exp “Cerebral Small Vessel Diseases”/ or exp leukoaraiosis/
3	1 or 2
4	exp “Antihypertensive Agents”/ or exp “Hypertension”/ or exp “Sodium Potassium Chloride Symporter Inhibitors”/ or exp “Bumetanide”/ or exp “Ethacrynic Acid”/ or exp “Furosemide”/ or exp “Sodium Chloride Symporter Inhibitors”/ or exp “Hydrochlorothiazide”/ or exp “Chlorothiazide”/ or exp “Bendroflumethiazide”/ or exp “Xipamide”/ or exp “Indapamide”/ or exp “Chlorthalidone”/ or exp “Metolazone”/ or exp “Diuretics, Potassium Sparing”/ or exp “Amiloride”/ or exp “Triamterene”/ or exp “Dihydropyridines”/ or exp “Amlodipine”/ or exp “Felodipine”/ or exp “Isradipine”/ or exp “Nicardipine”/ or exp “Nifedipine”/ or exp “Nimodipine”/ or exp “Nitrendipine”/ or exp “Nisoldipine”/ or exp “Nitrendipine”/ or exp “Diltiazem”/ or exp “Verapamil”/ or exp “Angiotensin-Converting Enzyme Inhibitors”/ or exp “Captopril”/ or exp “Enalapril”/ or exp “Fosinopril”/ or exp “Lisinopril”/ or exp “Perindopril”/ or exp “Ramipril”/ or exp “Cilazapril”/ or exp “Angiotensin Receptor Antagonists”/ or exp “Losartan”/ or exp “Valsartan”/ or exp “Atenolol”/ or exp “Metoprolol”/ or exp “Nadolol”/ or exp “Nebivolol”/ or exp “Oxprenolol”/ or exp “Pindolol”/ or exp “Propranolol”/ or exp “Timolol”/ or exp “Bisoprolol”/ or exp “Acebutolol”/ or exp “Celiprolol”/ or exp “Sotalol”/ or exp “Doxazosin”/ or exp “Phentolamine”/ or “Indoramin”/ or exp “Phenoxybenzamine”/ or exp “Prazosin”/ or exp “Ketanserin”/ or exp “Phentolamine”/ or exp “Labetalol”/ or exp “Hydralazine”/ or exp “Minoxidil”/ or exp “Mineralocorticoid Receptor Antagonists”/ or exp “Spironolactone”/ or exp “Clonidine”/ or exp “Guanabenz”/ or exp “Guanfacine”/ or exp “Methyldopa”/ or exp “Guanethidine”/ or exp “Mecamylamine”/ or exp “Magnesium Sulfate”/
5	(“torsemide” or “cilnidipine” or “mepirodipine” or “lacidipine” or “aranidipine” or “azelnidipine” or “benidipine hydrochloride” or “clevidipine” or “darodipine” or “efonidipine” or “manidipine” or “niguldipine” or “nilvadipine” or “quinapril” or “trandolapril” or “benazepril” or “zofenopril” or “imidapril” or “oxodipine” or “pranidipine” or “candesartan” or “eprosartan” or “irbesartan” or “olmesartan” or “telmisartan” or “azilsartan” or “fimasartan” or “esmolol” or “Terazosin” or “urapidil” or “carvedilol” or “aliskiren” or “eplerenone” or “moxonidine” or “lercanidipine”).rn.
6	(antihypertensive or “anti-hypertensive” or beta-blocker* or betablocker* or angiotensin* or “loop diuretic*” or “bumetanide ethacrynic acid” or furosemide or torsemide or “thiazide diuretic*” or epitizide or hydrochlorothiazide or chlorothiazide or bendroflumethiazide or xipamide or indapamide or chlorthalidone or metolazone or amiloride or triamterene or amlodipine or cilnidipine or felodipine or isradipine or lercanidipine or levamlodipine or nicardipine or nifedipine or nimodipine or nitrendipine or barnidipine or lacidipine or aranidipine or azelnidipine or benidipine or clevidipine or darodipine or efonidipine or manidipine or niguldipine or nilvadipine or nisoldipine or nitrendipine or oxodipine or pranidipine or diltiazem or verapamil or “ACE-inhibitor*” or captopril or enalapril or fosinopril or lisinopril or perindopril or quinapril or ramipril or trandolapril or benazepril or zofenopril or imidapril or cilazapril or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan or azilsartan or fimasartan or atenolol or metoprolol or nadolol or nebivolol or oxprenolol or pindolol or propranolol or timolol or bisoprolol or acebutolol or celiprolol or esmolol or sotalol or doxazosin or phentolamine or indoramin or phenoxybenzamine or prazosin or terazosin or tolazolin or ketanserin or urapidil or fentolamin or carvedilol or labetalol or hydralazine or minoxidil or aliskiren or eplerenone or spironolactone or clonidine or guanabenz or guanfacine or methyldopa or moxonidine or guanethidine or mecamylamine or magnesium sulfate or ((pharmacolog* or nonpharmacolog* or non-pharmacolog*) adj5 (intervention* or treatment* or therap* or management or strateg*))).ti,ab,kf.
7	4 or 5 or 6
8	3 and 7

Embase	
1	(exp "cerebrovascular disease"/ and (white matter lesion/ or vascular lesion/)) or exp leukoaraiosis/
2	(((“Lacunar stroke*” or “small vessel disease” or “Cerebral Microangiopath*” or “subcortical infarct*” or “White matter hyperintens*” or “Cerebral microbleed*” or “Brain atroph*” or “Small vessel cerebrovascular diseas*” or “Small vessel cerebrovascular disorder*” or SVD or “lacunar infarct*” or “silent brain infarct*” or “subcortical stroke*” or “subcortical cystic infarct*” or “cerebral lacunar lesion*” or “deep lacunar lesion*” or “subcortical lacunar lesion*” or “symptomatic lacunar lesion*” or “a symptomatic lacunar lesion*” or “Small vessel disease stroke” or “small deep infarct*” or “perforator territory infarct*” or “lacunar arteriopathy” or “white matter lesion*” or WML or “white matter hyperintensities” or WMH or leukoaraiosis or leucoaraiosis or “Virchow-Robin space*” or “etat crible” or “type 3 lacune*” or “white matter change*” or “WMC” or “changes in white matter” or “leukoencephalopathy” or “white matter disease” or “WMD” or “white matter damage” or (“perivascular space*” and (cerebr* or brain)) or (lacune* and (cerebr* or brain)) or (“deep infarct*” and (cerebr* or brain)) or (“deep stroke*” and (cerebr* or brain)) or microinfarct*) and (cerebr* or brain)) or “brain microbleed” or “chronic microbleed” or “silent microbleed” or “asymptomatic microbleed” or “cerebral microhemorrhage” or “cerebral microhaemorrhage” or “dot-like hemosiderin spot*” or “dot-like hemosiderin deposition” or “small vessel infarct*” or “small vessel stroke*” or “microscopic infarct*” or “brain volum*” or “cerebral volum*”).ti,ab,kw.
3	(“torsemide” or “cilnidipine” or “mepirodipine” or “lacidipine” or “aranidipine” or “azelnidipine” or “benidipine hydrochloride” or “clevidipine” or “darodipine” or “efonidipine” or “manidipine” or “niguldipine” or “nilvadipine” or “quinapril” or “trandolapril” or “benazepril” or “zofenopril” or “imidapril” or “oxodipine” or “pranidipine” or “candesartan” or “eprosartan” or “irbesartan” or “olmesartan” or “telmisartan” or “azilsartan” or “fimasartan” or “esmolol”or“Terazosin”or“urapidil”or“carvedilol”or“aliskiren”or“eplerenone”or“moxonidine”or“lercanidipine”).rn.
4	exp *antihypertensive agent/ or exp *hypertension/ or exp *loop diuretic agent/ or exp *thiazide diuretic agent/ or exp *potassium sparing diuretic agent/
5	(antihypertensive or “anti-hypertensive” or beta-blocker* or betablocker* or angiotensin* or “loop diuretic*” or “bumetanide ethacrynic acid” or furosemide or torsemide or “thiazide diuretic*” or epitizide or hydrochlorothiazide or chlorothiazide or bendroflumethiazide or xipamide or indapamide or chlorthalidone or metolazone or amiloride or triamterene or amlodipine or cilnidipine or felodipine or isradipine or lercanidipine or levamlodipine or nicardipine or nifedipine or nimodipine or nitrendipine or barnidipine or lacidipine or aranidipine or azelnidipine or benidipine or clevidipine or darodipine or efonidipine or manidipine or niguldipine or nilvadipine or nisoldipine or nitrendipine or oxodipine or pranidipine or diltiazem or verapamil or “ACE-inhibitor*” or captopril or enalapril or fosinopril or lisinopril or perindopril or quinapril or ramipril or trandolapril or benazepril or zofenopril or imidapril or cilazapril or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan or azilsartan or fimasartan or atenolol or metoprolol or nadolol or nebivolol or oxprenolol or pindolol or propranolol or timolol or bisoprolol or acebutolol or celiprolol or esmolol or sotalol or doxazosin or phentolamine or indoramin or phenoxybenzamine or prazosin or terazosin or tolazolin or ketanserin or urapidil or fentolamin or carvedilol or labetalol or hydralazine or minoxidil or aliskiren or eplerenone or spironolactone or clonidine or guanabenz or guanfacine or methyldopa or moxonidine or guanethidine or mecamylamine or magnesium sulfate or ((pharmacolog* or nonpharmacolog* or non-pharmacolog*) adj5 (intervention* or treatment* or therap* or management or strateg*))).ti,ab,kw.
6	1 or 2
7	3 or 4 or 5
8	6 and 7
9	(embase or elsevier or canadian).cr.
10	8 and 9

The Cochrane Library	
#1	([mh "Cerebral Small Vessel Diseases"] or [mh leukoaraiosis])
#2	(Lacunar stroke* or small vessel disease or Cerebral Microangiopath* or subcortical infarct* or White matter hyperintens* or Cerebral microbleed* or Brain atroph* or Small vessel cerebrovascular diseas* or Small vessel cerebrovascular disorder* or SVD or lacunar infarct* or silent brain infarct* or subcortical stroke* or subcortical cystic infarct* or cerebral lacunar lesion* or deep lacunar lesion* or subcortical lacunar lesion* or symptomatic lacunar lesion* or asymptomatic lacunar lesion* or Small vessel disease stroke or small deep infarct* or perforator territory infarct* or lacunar arteriopathy or white matter lesion* or WML or white matter hyperintensities or WMH or leukoaraiosis or leucoaraiosis or Virchow-Robin space* or etat crible or type 3 lacune* or white matter change* or WMC or changes in white matter or leukoencephalopathy or white matter disease or WMD or white matter damage or (perivascular space* and (cerebr* or brain)) or (lacune* and (cerebr* or brain)) or (deep infarct* and (cerebr* or brain)) or (deep stroke* and (cerebr* or brain)) or microinfarct* and (cerebr* or brain) or brain microbleed or chronic microbleed or silent microbleed or asymptomatic microbleed or cerebral microhemorrhage or cerebral microhaemorrhage or dot-like hemosiderin spot* or dot-like hemosiderin deposition or small vessel infarct* or small vessel stroke* or microscopic infarct* or brain volum* or cerebral volum*):ti,ab
#3	#1 or #2
#4	([mh "Antihypertensive Agents"] or [mh Hypertension] or [mh "Sodium Potassium Chloride Symporter Inhibitors"] or [mh Bumetanide] or [mh "Ethacrynic Acid"] or [mh Furosemide] or [mh "Sodium Chloride Symporter Inhibitors"] or [mh Hydrochlorothiazide] or [mh Chlorothiazide] or [mh Bendroflumethiazide] or [mh Xipamide] or [mh Indapamide] or [mh Chlorthalidone] or [mh Metolazone] or [mh "Diuretics, Potassium Sparing"] or [mh Amiloride] or [mh Triamterene] or [mh Dihydropyridines] or [mh Amlodipine] or [mh Felodipine] or [mh Isradipine] or [mh Nicardipine] or [mh Nifedipine] or [mh Nimodipine] or [mh Nitrendipine] or [mh Nisoldipine] or [mh Nitrendipine] or [mh Diltiazem] or [mh Verapamil] or [mh "Angiotensin-Converting Enzyme Inhibitors"] or [mh Captopril] or [mh Enalapril] or [mh Fosinopril] or [mh Lisinopril] or [mh Perindopril] or [mh Ramipril] or [mh Cilazapril] or [mh "Angiotensin Receptor Antagonists"] or [mh Losartan] or [mh Valsartan] or [mh Atenolol] or [mh Metoprolol] or [mh Nadolol] or [mh Nebivolol] or [mh Oxprenolol] or [mh Pindolol] or [mh Propranolol] or [mh Timolol] or [mh Bisoprolol] or [mh Acebutolol] or [mh Celiprolol] or [mh Sotalol] or [mh Doxazosin] or [mh Phentolamine] or [mh Indoramin] or [mh Phenoxybenzamine] or [mh Prazosin] or [mh Ketanserin] or [mh Phentolamine] or [mh Labetalol] or [mh Hydralazine] or [mh Minoxidil] or [mh "Mineralocorticoid Receptor Antagonists"] or [mh Spironolactone] or [mh Clonidine] or [mh Guanabenz] or [mh Guanfacine] or [mh Methyldopa] or [mh Guanethidine] or [mh Mecamylamine] or [mh "Magnesium Sulfate"])
#5	(antihypertensive or anti-hypertensive or beta-blocker* or betablocker* or angiotensin* or loop diuretic* or bumetanide ethacrynic acid or furosemide or torsemide or thiazide diuretic* or epitizide or hydrochlorothiazide or chlorothiazide or bendroflumethiazide or xipamide or indapamide or chlorthalidone or metolazone or amiloride or triamterene or amlodipine or cilnidipine or felodipine or isradipine or lercanidipine or levamlodipine or nicardipine or nifedipine or nimodipine or nitrendipine or barnidipine or lacidipine or aranidipine or azelnidipine or benidipine or clevidipine or darodipine or efonidipine or manidipine or niguldipine or nilvadipine or nisoldipine or nitrendipine or oxodipine or pranidipine or diltiazem or verapamil or ACE-inhibitor* or captopril or enalapril or fosinopril or lisinopril or perindopril or quinapril or ramipril or trandolapril or benazepril or zofenopril or imidapril or cilazapril or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan or azilsartan or fimasartan or atenolol or metoprolol or nadolol or nebivolol or oxprenolol or pindolol or propranolol or timolol or bisoprolol or acebutolol or celiprolol or esmolol or sotalol or doxazosin or phentolamine or indoramin or phenoxybenzamine or prazosin or terazosin or tolazolin or ketanserin or urapidil or fentolamin or carvedilol or labetalol or hydralazine or minoxidil or aliskiren or eplerenone or spironolactone or clonidine or guanabenz or guanfacine or methyldopa or moxonidine or guanethidine or mecamylamine or magnesium sulfate or ((pharmacolog* or nonpharmacolog* or non-pharmacolog*) Adj5 (intervention* or treatment* or therap* or management or strateg*))):ti,ab
#6	#4 or #5
#7	#3 and #6

BIOSIS	
1	(((Lacunar stroke* or small vessel disease or Cerebral Microangiopath* or subcortical infarct* or White matter hyperintens* or Cerebral microbleed* or Brain atroph* or Small vessel cerebrovascular diseas* or Small vessel cerebrovascular disorder* or SVD or lacunar infarct* or silent brain infarct* or subcortical stroke* or subcortical cystic infarct* or cerebral lacunar lesion* or deep lacunar lesion* or subcortical lacunar lesion* or symptomatic lacunar lesion* or asymptomatic lacunar lesion* or Small vessel disease stroke or small deep infarct* or perforator territory infarct* or lacunar arteriopathy or white matter lesion* or WML or white matter hyperintensities or WMH or leukoaraiosis or leucoaraiosis or Virchow-Robin space* or etat crible or type 3 lacune* or white matter change* or WMC or changes in white matter or leukoencephalopathy or white matter disease or WMD or white matter damage or (perivascular space* and (cerebr* or brain)) or (lacune* and (cerebr* or brain)) or (deep infarct* and (cerebr* or brain)) or (deep stroke* and (cerebr* or brain)) or microinfarct*) and (cerebr* or brain)) or brain microbleed or chronic microbleed or silent microbleed or asymptomatic microbleed or cerebral microhemorrhage or cerebral microhaemorrhage or dot-like hemosiderin spot* or dot-like hemosiderin deposition or small vessel infarct* or small vessel stroke* or microscopic infarct* or brain volum* or cerebral volum*).ti,ab,kw.
2	(antihypertensive or anti-hypertensive or beta-blocker* or betablocker* or angiotensin* or loop diuretic* or bumetanide ethacrynic acid or furosemide or torsemide or thiazide diuretic* or epitizide or hydrochlorothiazide or chlorothiazide or bendroflumethiazide or xipamide or indapamide or chlorthalidone or metolazone or amiloride or triamterene or amlodipine or cilnidipine or felodipine or isradipine or lercanidipine or levamlodipine or nicardipine or nifedipine or nimodipine or nitrendipine or barnidipine or lacidipine or aranidipine or azelnidipine or benidipine or clevidipine or darodipine or efonidipine or manidipine or niguldipine or nilvadipine or nisoldipine or nitrendipine or oxodipine or pranidipine or diltiazem or verapamil or ACE-inhibitor* or captopril or enalapril or fosinopril or lisinopril or perindopril or quinapril or ramipril or trandolapril or benazepril or zofenopril or imidapril or cilazapril or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or valsartan or azilsartan or fimasartan or atenolol or metoprolol or nadolol or nebivolol or oxprenolol or pindolol or propranolol or timolol or bisoprolol or acebutolol or celiprolol or esmolol or sotalol or doxazosin or phentolamine or indoramin or phenoxybenzamine or prazosin or terazosin or tolazolin or ketanserin or urapidil or fentolamin or carvedilol or labetalol or hydralazine or minoxidil or aliskiren or eplerenone or spironolactone or clonidine or guanabenz or guanfacine or methyldopa or moxonidine or guanethidine or mecamylamine or magnesium sulfate or ((pharmacolog* or nonpharmacolog* or non-pharmacolog*) adj5 (intervention* or treatment* or therap* or management or strateg*))).ti,ab,kw.
3	1 and 2

Supplemental methods II. Logarithmic transformation

For a meta-analysis the raw data in each study does not need to be normally distributed. Only the distribution of the mean should be normally distributed. Any logarithmic mean and variability measures should therefore be transformed to the raw data. This can be done with the following formula:[187]

$$\bar{x}'_i = \exp\left(\bar{z}_i + \frac{s^2_{z,i}}{2}\right) \quad (i = 1, 2)$$

$$s'_{x,i} = \sqrt{(\exp(s^2_{z,i}) - 1)\exp(2\bar{z}_i + s^2_{z,i})} \quad (i = 1, 2)$$

x indicates the raw mean; z, logarithmic mean; s, raw SD; z, logarithmic SD.

This formula led to the following transformation of data on white matter hyperintensities (WMH) at follow-up and progression during follow-up from the ACCORD trial:

Mean WMH at follow-up, intervention: $\exp(0.62 + (0.41^2/2)) = 2.02$

SD WMH at follow-up, intervention: $\sqrt{(\exp(0.41^2 - 1) \times \exp(2 \times 0.62 + 0.41^2))} = 0.87$

Mean WMH at follow-up, control: $\exp(0.77 + (0.42^2/2)) = 2.36$

SD WMH at follow-up, control: $\sqrt{(\exp(0.42^2 - 1) \times \exp(2 \times 0.77 + 0.42^2))} = 1.04$

Mean WMH progression, intervention: $\exp(0.53 + (0.41^2/2)) = 1.85$

SD WMH progression, intervention: $\sqrt{(\exp(0.41^2 - 1) \times \exp(2 \times 0.53 + 0.41^2))} = 0.79$

Mean WMH progression, control: $\exp(0.68 + (0.42^2/2)) = 2.16$

SD WMH progression, control: $\sqrt{(\exp(0.42^2 - 1) \times \exp(2 \times 0.68 + 0.42^2))} = 0.95$

Supplemental table I - Cochrane risk of bias assessment

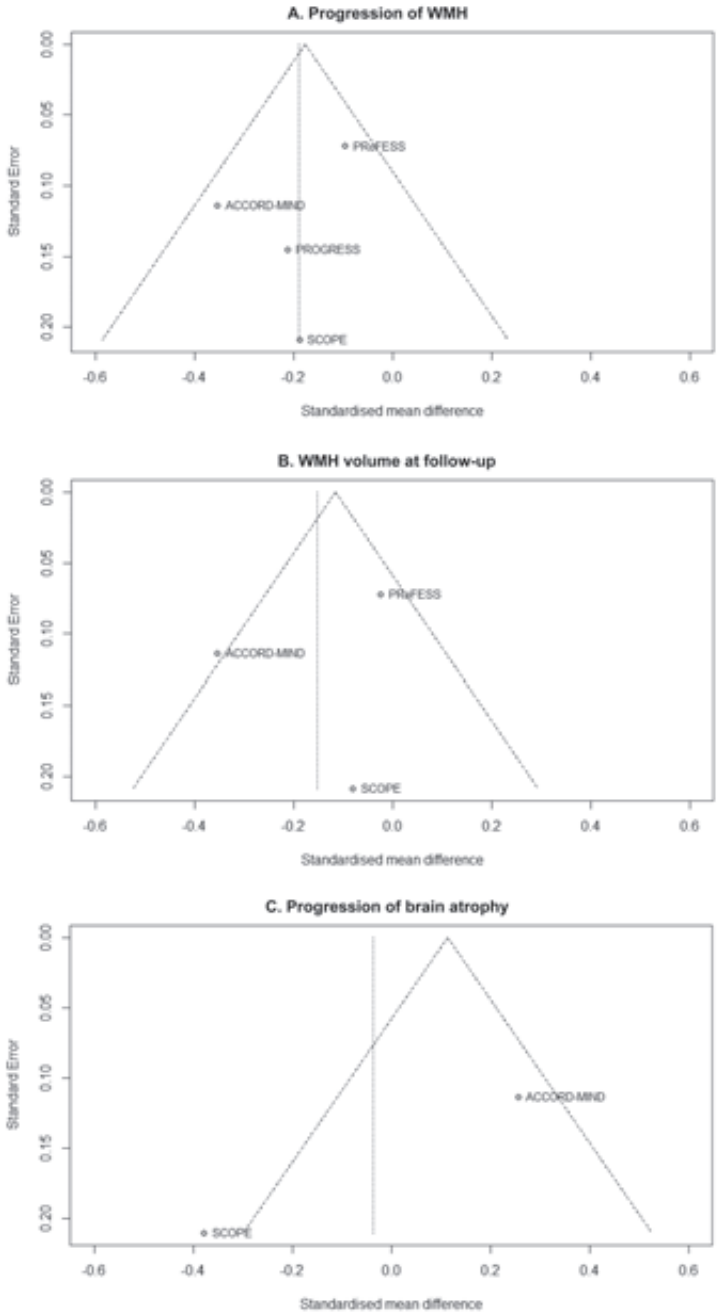
	ACCORD	PROFESS	PROGRESS	SCOPE
Random sequence generation (selection bias)	+	+	+	+
Allocation concealment (selection bias)	+	+	+	+
Blinding of participants and personnel (performance bias)	-	+	+	+
Blinding of outcome assessment (detection bias)	+	+	+	?
Incomplete outcome data (attrition bias)	+	?	+	+
Selective reporting (reporting bias)	?	+	+	?
Other bias	+	+	+	?

The green plus-signs indicate a low risk of bias, the yellow question mark-signs indicate an unclear risk of bias, and the red minus-sign indicates a high risk of bias. In the ACCORD trial participants and treating physicians could not be blinded.[189,192] This was inherent to the design of the intervention; i.e. intensive blood pressure (BP) control with a target SBP <120 mmHg. In the PROFESS trial no explanation was given for the participants that were lost to follow-up thereby increasing the risk of attrition bias.[188] In the SCOPE trial no selection criteria for the MRI substudy were given, no declaration of interest was presented and it was unclear whether the outcome assessment was blinded to treatment allocation.[190]

Supplemental table II - Methods of SVD determination

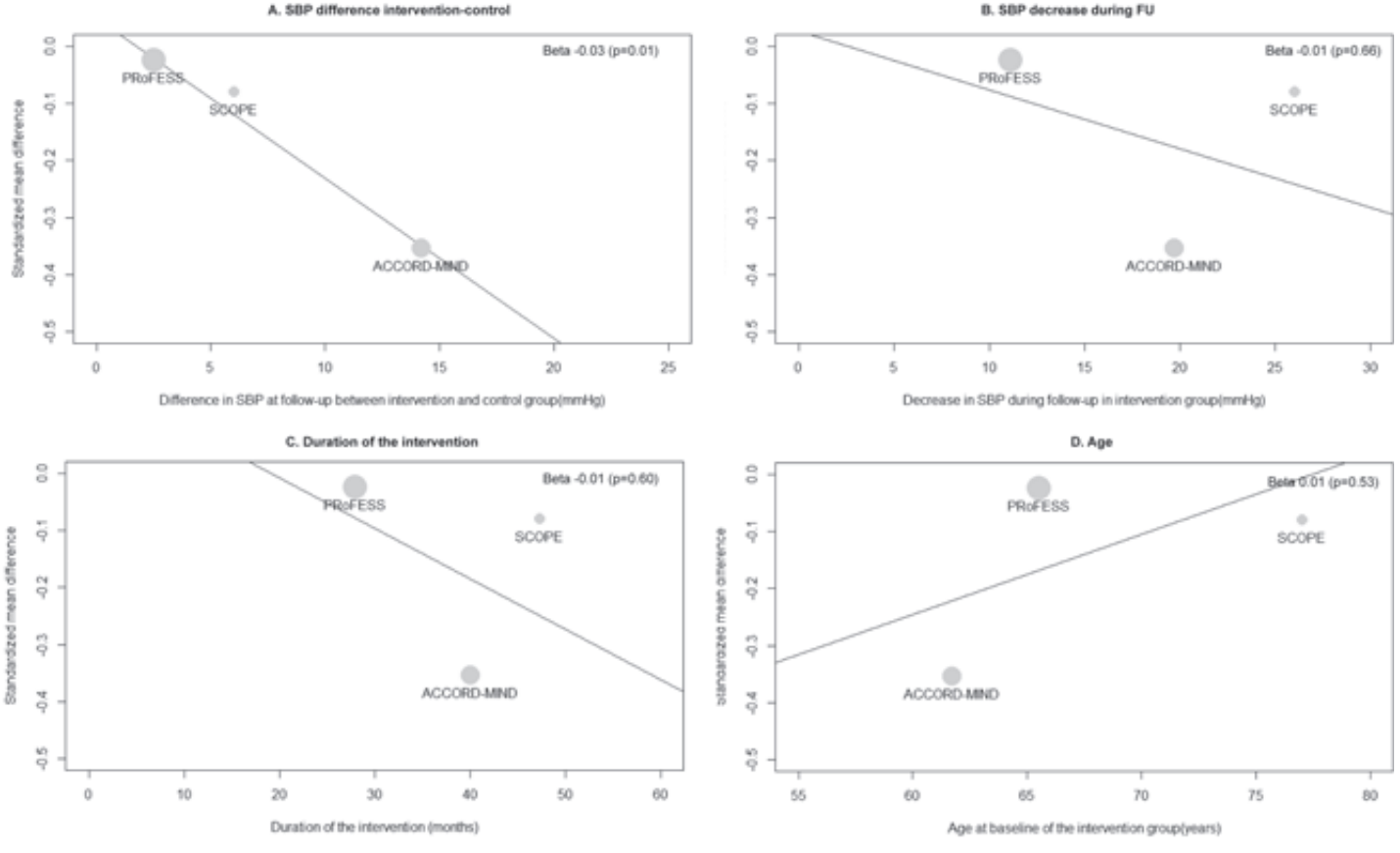
Trial	Sequences	Field strength (Tesla)	Thickness of slices (mm)	Scan comparability	Method of WMH measurement	Method of brain atrophy measurement
ACCORD-MIND	T1, T2, FLAIR, 3D FSPGR	1.5	1.5 - 3 mm	Yes	Automatic volumetric measurement	Automatic volumetric analysis of TBV
PRoFESS	T1, T2, FLAIR, DWI	n.r.	n.r.	n.r.	Periventricular: Manual rating scale from the Rotterdam Scan Study** Subcortical: Manual volumetric measurement †	n.r.
PROGRESS	T1, T2	1.0 T or 1.5 T	1.4-5 mm	Yes	Visual volumetric measurement by manual delineation of each new WMH during follow-up	n.r.
SCOPE	T1, T2, FLAIR	1.5 T	1.7 – 5 mm	Yes	Automatic volumetric measurement (SPM99)	Semi-automated measurement with Brain Boundary Shift Integral technique*

Scan comparability indicates whether the authors stated that the magnetic resonance imaging at baseline was comparable to the one at follow-up. ***** *The Brain Boundary Shift Integral technique calculates the distance by which the brain/CSF boundary has shifted between scans to quantify rates of atrophy.* ** *Periventricular WMHs in the PRoFESS trial were visually rated as 0 (none), 1 (pencil-thin lining), 2 (smooth halo), or 3 (large confluent) in 3 different regions of interest; these scores were added up (range, 0–9).* † *The volume of subcortical WMHs in the PRoFESS trial was approximated according to the presence and rating of maximum diameter of WMH as 0 (none), 1 (1–3 mm), 2 (3–10 mm), or 3 (10 mm). Mnt indicates month; mm, milimeter; WMH, white matter hyperintensities; FLAIR, fluid attenuation inversion recovery; DWI, diffusion weighted imaging; n.r. not reported; FSPGR, fast spoiled gradient echo; TBV, total brain volume.*



Supplemental figure I - Funnel plot on progression of WMH (A), WMH volume at follow-up (B), and progression of brain atrophy (C)

WMH indicates white matter hyperintensities.



Supplemental figure II - Meta-regression on the influence of SBP, intervention duration and age on the effect of AHM on WMH volume at follow-up

WMH indicates white matter hyperintensities; SBP, systolic blood pressure; FU, follow-up

GENERAL DISCUSSION

10

This thesis focuses on blood pressure (BP) management to prevent dementia. In **part I** I studied the relation between BP in late life and dementia, with a meta-analysis on the preventive effect of BP-lowering interventions and analyses on specific classes of antihypertensive medication (AHM) and visit-to-visit BP variability. In addition, I performed interviews with general practitioners (GPs) on (de)prescription of AHM. In **part II** I explored several methodological aspects in dementia prevention trials. This includes analyses on the usability of a modifiable dementia risk score as tool to select an optimal target population. I interviewed trial participants on reasons for participation in a prevention trial and engagement with an interactive internet platform. Finally, I completed a meta-analysis on the effect of AHM on progression of cerebral small vessel disease (SVD), to assess its usefulness as intermediate outcome. In this chapter I will discuss the findings within the framework of other relevant research and discuss its' implications for clinical practice and future research.

PART I – BLOOD PRESSURE IN LATE LIFE AND DEMENTIA

Historical perspective

Until half a century ago BP and dementia were not known to be associated and were viewed as two separate domains. To better understand developments leading to the research questions addressed in this thesis, I briefly shed some light on the historical context of both domains.

The ancient Egyptians already described the concept of dementia around 2000 B.C. Until the early eighteenth century many different terms were used to describe dementia, such as imbecility, senility or simplicity; reflecting the view of society, that long considered dementia a psychosocial problem.[204] The term dementia is derived from the Latin term *demens*, which loosely translated means 'without mind'.[204] In the 17th century, Thomas Willis described a correlation between stroke and dementia, knowledge that later led to the concept of vascular dementia.[205] Alzheimer's disease was introduced much later, in 1910, with the clinical and pathological descriptions made by Alois Alzheimer on his patient, mrs. Auguste D.[206] She presented with severe cognitive impairment, delusions and hallucinations, and, at autopsy of the brain, had loss of neurons and the presence of senile plaques and neurofibrillary tangles. These distinct features were later considered to characterize Alzheimer's disease.

The research field on BP is relatively young. Until the early twentieth century a progressive increase in BP was considered part of normal aging.[207] After the death of Franklin D. Roosevelt in 1945 due to a haemorrhagic stroke, with a BP of 300/190 mmHg, the United States government declared high BP a threat to national health.[208] The first observational studies and trials in the subsequent years focused on the detrimental effects of a high

diastolic BP. Twenty years later, trials on high systolic BP followed.
Both research domains merged in 1947 with the first case studies linking hypertension to cognitive function.[209] Several cross-sectional and later also prospective descriptive studies followed. These studies first focussed on the association of BP with vascular dementia, but in the 1990s also an association with Alzheimer's disease became apparent.[210]

Antihypertensive medication classes

Even though the association between midlife hypertension and dementia is strong, in **chapter two** we have shown that randomised controlled trails (RCTs) have not conclusively proven that lowering BP by AHM and/or lifestyle changes can prevent dementia. Our results in **chapter three** indicate that there might be an AHM class-specific effect in preventing dementia, with lower risks in participants using calcium channel blockers (CCBs) and/or angiotensin receptor blockers (ARBs). However, we could not confirm this class-specific effect in our systematic review (**chapter two**). A network meta-analysis was deemed unreliable, as there were too few trials for the different AHM classes and these were all placebo-controlled, limiting the possibilities of indirect comparisons. Paired meta-analysis (including only direct comparisons) did not indicate a favourable AHM class, aside from one trial on CCBs with a high risk of publication bias.
There are several cerebrovascular and neurodegenerative mechanisms that could explain the class-specific effect described in **chapter three** (further elaborated on in the subsequent paragraph).[59] Another hypothesis for the observed association is that it is not based on a physiological class-difference, but rather a difference in the stability of BP control.[67] A way of assessing this is with visit-to-visit BP variability. However, we did not find an association between a higher BP variability and an increased risk of dementia (**chapter four**). In a French cohort study, which found an association between visit-to-visit variability and risk of dementia, the AHM class effect appeared independent of BP variability.[67,78] Another way to define BP control is by looking at the biological half-life of different AHM, as drugs with a longer biological half-life probably give a more stable BP control and this may potentially lower the risk of dementia.[211] We have assessed this within the *Prevention of Dementia by Intensive Vascular Care* (preDIVA) study population with AHM at baseline, by comparing participants using AHM with a longer half-life, to participants using AHM with a shorter half-life (divided at the median half-life). Participants using AHM with a longer half-life did not have a lower risk of dementia (hazard ratio 0.96, 95% confidence interval 0.66-1.39; unpublished data). Based on these findings, the association between CCBs and/or ARBs and dementia does not appear to be the consequence of a difference in stability of BP control, thereby increasing the likelihood that there is indeed a physiological class effect.
Currently, researchers study the class-specific effect of AHM on dementia and cognitive decline with a systematic review and harmonised meta-analysis of observational studies

and RCTs.[212] This meta-analysis will address class-specific effects in a larger and more diverse study population. However, confounding by indication is still an important potential source of bias, as mainly observational studies are included.[213] An RCT on potential AHM class effects on dementia risk is required to make conclusive recommendations for clinical practice (as described in further detail in the final paragraph of this chapter).

MRI characteristics as intermediate marker

Cerebral SVD has been identified as mediator in the association between hypertension and cognitive impairment via atherosclerosis.[214] Contrary to the previously mentioned neutral findings of BP-lowering interventions to prevent dementia (**chapter two**), we found that AHM could prevent progression of white matter hyperintensities (WMH), one of the markers of cerebral SVD (**chapter nine**). An effect of AHM on brain atrophy could not be found and no trials assessed the effect on the other markers of SVD (lacunes, microbleeds, enlarged perivascular spaces and acute small subcortical infarcts). A similar WMH-dementia mismatch was seen in the *Evaluation of Vascular Care in Alzheimer's Disease* (EVA) trial,[215] with a beneficial effect of vascular care on WMH progression in patients with early Alzheimer's disease and cerebrovascular lesions, but no effect on cognition or disability. Results from the preDIVA magnetic resonance imaging (MRI) sub-study (preDIVA-M) were in line with the primary results of the preDIVA trial, showing no effect of the intervention on WMH progression.[202] Secondary analyses in preDIVA-M suggested that treatment effect was larger in participants with higher WMH volume at baseline.

It is intriguing that despite the effect of AHM on (one of) the mediator(s) no effect on dementia was found. Perhaps influencing only one marker of cerebrovascular pathology is not sufficient to yield a clinical effect, especially since dementia in older persons is often associated with mixed neurodegenerative and cerebrovascular pathology. In our systematic review in **chapter two** many trials had an intervention duration <5 years, which may be too short to detect an effect on dementia, while a two to four year follow-up seems adequate to detect an effect on WMH (**chapter nine**). Finally, competing risk of death may have influenced the results on dementia more than on WMH. BP-lowering interventions decrease the risk of mortality and therefore cause an imbalance in the number, and possibly also the age and cardiovascular risk, of people at risk of dementia or WMH progression. This selective dropout may have a stronger effect on the dementia analysis as this requires longer follow-up.

The preDIVA-M substudy provides the opportunity to explore some of our hypothesized mechanisms proposed in **chapter three** and **four** on the association of dementia with different AHM-classes and visit-to-visit BP variability. One of the pathways that potentially accounts for the association between CCBs and/or ARBs and dementia in **chapter three** is an increase in cerebrovascular perfusion.[59] With the MRI data of preDIVA-M we were able to

assess the level of cerebral perfusion in participants with specific AHM-classes. Although the number of participants using CCBs or ARBs was small (n=35), a substantially higher cerebral perfusion was found in comparison to participants using other AHM (unpublished). CCBs and ARBs are also suggested to influence amyloid β depositions. A brain autopsy study showed that ARB use was associated with less amyloid depositions.[216] Similar autopsy studies are not available for CCBs.[59] In **chapter four** we found that high visit-to-visit BP variability was not associated with a higher risk of incident dementia. Our results are in contrast with two other observational studies where an association between visit-to-visit or day-to-day BP variability and dementia was found.[78,217] One of the potential pathways of this association would be that BP variability causes microvascular damage which leads to atherosclerosis and ultimately (progression of) cerebral SVD. Within the preDIVA-M sub-study, we found an association between visit-to-visit BP variability and WMH progression (β 0.04; 95% CI 0.01-0.07; p-value<0.01; unpublished data). Another possible explanation may be that arterial stiffness causes a higher BP variability and higher risk of dementia, as it is associated with amyloid β depositions.[85]

Potential disadvantages of a low or declining BP

Observational studies indicate a J-shaped association between BP and several measures of poor outcome, such as cardiovascular disease (CVD), cognitive decline and mortality (see also chapter one, Figure 1).[20,207,218] Whether a low BP is indeed causally related to a higher risk of poor outcome, is only known for diastolic BP and ischemic coronary heart disease; this is conceivable, as coronary perfusion occurs mainly during diastole.[207] It is less evident whether such a causal relation is also present for systolic BP or with different outcome measures. A recent individual participant data (IPD) meta-analysis based on two RCTs among almost 14 thousand participants, showed that people treated with a target systolic BP <120 mmHg had a lower risk of CVD within three years than those with a target systolic BP <140 mmHg.[219] Interestingly, the investigators found that the extent of the deviation from the target BP was an important marker for CVD in both treatment arms. This supports the reverse causality-hypothesis, which states that a low or declining BP is a marker of unfavourable patient characteristics and, with that, marker of poor outcome. The reverse causality-hypothesis is also supported by studies on BP trajectories, which show that BP already declined 14 to 18 years prior to death or dementia.[75,220] It is not yet known whether such a decline is still amenable to treatment.

The optimal BP treatment for people in late life is unknown. Trials have shown that AHM can still prevent CVD and mortality in older people and that a target systolic BP as low as <120 mmHg may be preferable.[92,94] However, the generalizability of these trial populations to the general population, including multi-morbid and frail people, is questionable as it is often a selection of healthier older people.[221] Also, with increasing age, treatment priorities

shift from preventing morbidity and mortality to maintaining quality of life and functional independence.[222] To study how GPs deal with the uncertainties regarding optimal BP treatment for people in late life, we interviewed fifteen Dutch GPs (**chapter five**). We explored their routines and considerations when prescribing and deprescribing (decreasing dosages or discontinuing) AHM. GPs indicated that they often continued AHM and felt restrained in deprescribing. Factors that influenced this restrained approach in reducing AHM were anticipated regret (that is, fear to 'cause' a stroke by deprescribing) and the feeling that continuation of treatment required less justification. GPs felt insufficient guidance from current guidelines and they would appreciate clear indicators for deprescription.

The evidence to deprescribe AHM remains limited. A trial published in the 1990's showed that discontinuation of long-term diuretic use increases the risk of heart failure within six months.[223] In the 20 years thereafter no new trials were published, until 2015 when the *Discontinuation of Antihypertensive Treatment in Elderly People* (DANTE) trial was published.[24] In this RCT AHM was discontinued or continued among people 75 years and older with mild cognitive deficits. Within a relative short follow-up period of 16 weeks, no benefit on cognitive, psychological, or general daily functioning was seen, but overall deprescription was safe during the short study period. A recent Cochrane review confirmed the limited available evidence on the effectiveness of AHM withdrawal on cognitive decline.[23] For clearer directives, a deprescription trial with a longer follow-up duration and careful event and outcome monitoring is required. Such a trial could, for example, include frail older adults or older people with a decreasing BP despite stable AHM use. Deprescription in combination with lifestyle advice seems preferable.[224] Outcome measures such as those used in the DANTE trial are probably most appropriate, as cognitive, psychological and physical functioning are of increasing importance with increasing age and they can be affected by a cardiovascular event.

Clinical implications

Our two systematic reviews on the efficacy of BP-lowering interventions to prevent dementia (**chapter two**) and cerebral SVD (**chapter nine**) will not directly change clinical practice, as BP-lowering interventions are already widely implemented to prevent CVD and mortality. More guidance is required on the indication, intensity and method of BP treatment for older people (**chapter five**). The current cardiovascular risk management guideline for Dutch GPs supports diuretics or CCBs as first choice treatment for older people.[106] The results as presented in **chapter three** may suggest CCBs should be favoured over diuretics. However, as this result is based on an observational study and there is also observational evidence in favour of diuretics,[67] there appears to be insufficient evidence to recommend changes to the current guideline. A trial with head-to-head comparison of AHM classes among older people could yield more evidence for a better-balanced choice for either AHM class (as described

in further detail in the final paragraph of this chapter). Evidence on the association between high visit-to-visit BP variability and an increased risk of CVD (**chapter four**) is consistent in current literature.[27] Although a causal relation is not yet established, taking visit-to-visit variations in BP into account to minimize variability appears rational. Such an approach could also alert physicians to a declining BP, which is associated with poor outcome. BP variability or a declining BP are currently not taken into account by Dutch GPs when (de)prescribing AHM (unpublished data from the interviews presented in chapter five). In **chapter five** we showed that the uncertainty about the net benefit of AHM deprescription, GPs' propensity to continue prescribing unchanged fuelled. As approximately a third of people in late life receive potentially inappropriate medication,[225] more support in making the decision to reduce AHM is necessary. While an AHM deprescription trial with longer follow-up is needed to provide clearer evidence on the advantages and disadvantage of deprescribing, clinical practice could already benefit from increased awareness of the possibility to reduce AHM among doctors and patients. A step in this direction is the recently published Dutch guideline that states deprescription in frail older adults should be considered in case of possible side-effects or limited life expectancy.[226] Shared decision making can aid in making better-informed decisions, by discussing the pros and cons of treatment with the patient and inquiring patients' wishes and priorities. Patients have indicated to appreciate such an open conversation about medication use.[227]

PART II – METHODOLOGICAL CHALLENGES IN PREVENTION TRIALS

Methodological considerations in the preDIVA trial

In the preDIVA trial no overall beneficial effect was found of intensive vascular care, among community-dwelling older people, on the primary outcome dementia and secondary clinical outcomes CVD and mortality.[16] One potential explanation for the neutral result is limited contrast between the intervention and control group. In particular, a pronounced decrease in systolic BP of 15-20 mmHg after baseline was observed in both treatment groups. This could have been caused by an improvement in the standard level of cardiovascular care during the trial, with a stronger focus on primary prevention after the 2011 guideline update.[106] Another explanation for the pronounced BP decline was that GPs were notified when a high BP was observed, which was the case in approximately three quarters of the participants at baseline,[62] and they probably acted accordingly. As it is considered unethical to not notify participants and/or their physician when an un(der)treated risk factor is detected, the only way to avert this is by not measuring BP at baseline. Hawthorne effects could have also influenced the results, which indicates that participants and health care providers could have changed their behaviour simply because they participated in a study.[228] Additionally, the preDIVA population could have been too old for the intervention

to have a preventive effect. The optimal timing for a dementia prevention trial is unclear. The window of opportunity decreases with increasing age, while the incidence of dementia increases.[28]

Another potential explanation for the neutral result of preDIVA is the unselected population at baseline, including participants with a low and high dementia risk. Although this is a pragmatic choice that improves generalizability and opportunities for implementation, it reduces the preventive room for improvement, as it is not possible to substantially reduce a risk that is already low. In a predefined subgroup analysis, a significant beneficial effect of the intervention on dementia incidence was found among participants with untreated hypertension at baseline who were adherent to the subsequent intervention.[16] In **chapter six** we assessed whether we could also find such a responsive group by selecting participants based a dementia risk score with multiple modifiable risk factors, the *LIfestyle for BRAin health* (LIBRA) index.[12] Contrary to our hypothesis, we found a trend towards a beneficial effect in participants with a low LIBRA index. Certainly this small effect should not be over-interpreted, but an interesting hypothesis may be that a high modifiable risk does not necessarily mean there is a high potential for change. A score designed as selection tool for prevention trials should combine a risk estimation with an estimation on whether adequate care is given for those risk factors (that is, their potential for change). That way a person with a systolic BP of 130 mmHg while using AHM, will less likely be recruited than a person with un(der)treated hypertension with a systolic BP of 160 mmHg, who may have a greater potential to benefit from the intervention.

In **chapter three** and **four** we studied the preDIVA dataset as if it were an observational cohort. As preDIVA is an RCT, these analyses may have suffered from various forms of bias. In general, external validity of RCTs is weaker than observational studies due to more pronounced selection bias at recruitment.[172] This seems to be of limited influence on preDIVA due to the general population approach and limited exclusion criteria, which resulted in a 52% participation rate of those who were invited. Comparison of preDIVA characteristics at baseline with national (cohort) data suggests that the preDIVA population is largely representative of the Dutch general population aged 70-78 years.[72] What could have affected the external validity of our results was selective drop-out of frail or cognitively impaired participants. As dementia was defined as clinical diagnosis and information on this outcome was available for 3454 (98%) participants,[229] it is unlikely that this drop-out affected our primary outcome much. However, it could have influenced results on cognition and selection of participants for the BP variability analyses, as we could only include participants who were present at ≥3 visits to reliably estimate variability. This could have led to a selection of relatively healthy participants. Another potential source of bias is that the natural disease course of dementia may have been altered by the intensive vascular care and/or Hawthorne effect, potentially influencing the association of dementia with AHM class or BP variability.

Pre-defined subgroup analyses did not show any differences in the association based on randomisation group. However, this may be because of the limited contrast between the intervention and control group.

Methodological considerations in the HATICE trial

As part of the *Healthy Ageing Through Internet Counselling in the Elderly* (HATICE) project, an international RCT assessing the effect of an interactive internet platform for cardiovascular self-management has taken place.[17] As primary outcome the intervention effect on cardiovascular risk will be assessed and as one of the secondary outcomes the effect on cognition. In contrast to the general population approach used in the preDIVA trial, in the HATICE trial high-risk participants have been recruited based on the presence of ≥2 cardiovascular risk factors (such as hypertension or lack of physical exercise), and/or a history of CVD, and/or a diagnosis of diabetes.[17] The generalizability of the trial is strengthened by recruiting participants from three European countries; the Netherlands, Finland and France. We explored the reasons for participation in HATICE to improve recruitment of future trials in **chapter seven**. The main reasons for participation were altruism, to improve one's lifestyle and to benefit from additional medical monitoring. The interviews revealed interesting cross-country differences in views on health care and how this influenced the decision to participate. For example, Finnish participants expressed low satisfaction with the availability of preventive primary health care and, potentially as a result, considered the medical monitoring aspect of HATICE highly relevant. French participants were concerned for their own wellbeing with increasing age, as they viewed care for, and quality of life of, the oldest of old below standard. They participated in HATICE to improve the overall care for oldest of old. As shown in **chapter eight** the reason for participation was often related to expectations of the platform and level of initiative in using the platform, with altruistic participants expecting fewer personal benefits and showing a tendency to use the platform in a more reactive way. These and other factors that influence engagement with the HATICE platform were further explored in **chapter eight** with semi-structured interviews among Dutch HATICE intervention participants. For both initial and sustained engagement, personal contact with the coach appeared pivotal. Comparable results were also found in a qualitative study among preDIVA participants.[148] While striving for concordant self-management (that is, when a person is enabled to maintain a healthy lifestyle independent from additional support) we noticed a reactive use of the HATICE platform in response to emails or reminders. This could imply a level of dependence on the platform and/or their coach. That may not be ideal, but perhaps inevitable and could still evoke lifestyle changes and potentially lower the cardiovascular risk. The final end visits in the HATICE trial have been completed in February 2018.

Ongoing BP trials to prevent dementia

The systematic review presented in **chapter two** provides a clear overview of the published BP trials with dementia as primary or secondary outcome. To make well-informed recommendations for future research we should also take into consideration the knowledge that will be acquired in currently ongoing trials. An important ongoing BP management trial with dementia, cognition and cerebral SVD as outcomes is the *Systolic Blood Pressure Intervention Trial Memory and Cognition in Decreased Hypertension* (SPRINT MIND).[199] The SPRINT trial showed a beneficial effect of intensive BP lowering (target systolic BP <120 mmHg versus <140 mmHg) on incident CVD and mortality in 9361 people with a systolic BP ≥130 mmHg at baseline and an increased cardiovascular risk, but without diabetes. Of all SPRINT participants data on incident dementia over five years will be gathered. In a subgroup also the rate of global cognitive decline and cerebral SVD progression will be measured.[199] Intensive BP control could potentially prevent dementia, but, given the J-shaped association, a reverse outcome is also imaginable. It will be interesting to see if the results on dementia, cognition and SVD are in line with one another or present an SVD-dementia mismatch (as previously discussed). The mixed pathology of dementia could still cause a mismatch, but the influence of competing risk of death might be smaller due to the relative young study population (mean age of 68 years at baseline). An ongoing trial that combines target BP with a multi-domain approach is the *European Society of Hypertension-Chinese Hypertension League Stroke in Hypertension Optimal Treatment* trial.[230] This is a 3 × 2 factorial design comparing three systolic BP targets (<125 mmHg, 125-135 mmHg and 135-145 mmHg) and two low-density lipoprotein cholesterol targets (<1.8 mmol/L and 1.8-2.8 mmol/L). 7500 patients aged ≥65 years with hypertension and a recent stroke or transient ischemic attack will be included. The primary outcome is stroke after four years and secondary outcomes are dementia and cognitive decline. An ongoing trial that might give more insight into the class-specific effect of CCBs is the *Nimodipine Preventing Cognitive Impairment in Ischemic Cerebrovascular Events* (NICE) trial.[231] This Chinese trial assesses the effect of nimodipine in the acute phase after an ischemic stroke to prevent mild cognitive impairment at six months. Their hypothesis is that nimodipine can increase cerebral perfusion and thereby reduce neurological deficits after acute ischemia. This may, however, not be the same protective mechanism as that in the general population of older people.

Intermediate outcome measures

PreDIVA is the first prevention trial with dementia as primary outcome. This is generally deemed too challenging as, due to the slow disease process of dementia, such trials need a relative long follow-up duration and large sample size to detect an effect. Most of the ongoing and future trials will therefore only include dementia as secondary outcome

measure and will most likely be underpowered to demonstrate an effect. Therefore, to come to more robust conclusions on the effects of cardiovascular prevention on dementia incidence, combining the data of several trials in a meta-analysis, preferably an IPD meta-analysis, may be the best way forward. The HATICE consortium has laid the groundwork for such an IPD by creating a shared data platform with preDIVA, *Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability* (FINGER) and *Multidomain Alzheimer Preventive Trial* (MAPT).[14,15,232] When long-term follow-up on dementia becomes available from FINGER and MAPT, the first IPD meta-analysis on prevention of dementia can be performed. In such an IPD meta-analysis a competing risk analysis can be performed to give more insight into competing risk of death as potential source of bias, which we were not able to do in our meta-analysis with aggregated data (**chapter two**).

Given the restrictions on using dementia as primary outcome, researchers have the difficult task of choosing an intermediate outcome measure for prevention trials with relatively short follow-up periods. In the HATICE trial a composite score including systolic BP, body-mass index and low-density lipoprotein cholesterol was chosen as primary outcome measure.[17] Arguments in favour of choosing this composite score are that it captures the intervention targets that are objectively measurable, no existing cardiovascular risk score was deemed appropriate for this population, and an intervention effect could be measurable within 18 months. This in contrast to, for example, an effect on CVD which would be a clinically more relevant endpoint. Another, more often used, intermediate outcome is cognitive function. As cognitive decline is one of the core symptoms preceding dementia, it seems rational to use this as an intermediate outcome measure, but interpretation can be challenging due to a poor signal to noise ratio or learning effects, especially when cognitive training is included in the intervention. In addition it is unclear which cognitive tests are best suited for dementia prevention trials. Cognition can be measured with short, global tests such as the Mini-Mental State Examination (MMSE), however the MMSE is designed as screening instrument rather than a test to measure change of cognition over time and is not very specific. Use of the MMSE in more sensitive analyses, such as the linear mixed-models used in **chapter four and six**, can show small differences that may be statistically significant but are likely not clinically relevant.[64] An extensive neuropsychological test battery is time consuming and could be considered burdensome. To limit the burden on participants a composite score could be used including only a few cognitive tests sensitive to early symptoms of dementia.[233] Finally, markers of cerebral SVD have been proposed as intermediate outcome. As the causal pathway of cardiovascular risk reduction to prevent dementia is likely mediated by cerebrovascular lesions, it would seem plausible to use cerebral SVD as intermediate outcome. In **chapter nine** we have shown that AHM can prevent progression of WMH. Before WMH can be reliably used as intermediate outcome measure, it should be confirmed that an effect on WMH progression is a proxy for an effect on dementia. Additionally, as an

MRI scan is not always easily available, is costly and can be a burden on participants, one of the other more pragmatic outcome measures might be preferable.

Towards a future prevention trial

I would like to conclude this chapter by making recommendations for the design of a future dementia prevention trial, based on the knowledge acquired in this thesis. In my opinion an RCT studying the class-specific effect of CCBs would be most valuable. Assessing the effect of CCBs instead of ARBs seems more feasible and relevant to daily practice, as the preferred first-choice AHM classes for older people without a history of CVD are diuretics or CCBs (based on the Dutch cardiovascular risk management guideline).[106] In clinical practice Dutch GPs do not appear to have clear preference for a specific AHM class and treatment choices are mainly based on previous experiences with specific drugs (unpublished data from the interviews presented in chapter five). A randomised intervention with CCBs, therefore, seems achievable. As dihydropyridine CCBs, such as amlodipine and nifedipine, can effectively penetrate the blood-brain barrier these would be preferable to a non-dihydropyridine CCB such as verapamil.[70] Choice of the control condition is more difficult. An option is to take any other AHM as control condition and leave it up to the treating physician which AHM class (other than CCBs) to choose, as the clinically most relevant question is what the preferred AHM class would be when AHM is indicated. This will probably most often be diuretics, as these are equal in rank to CCBs from the perspective of hypertension treatment. However, as diuretics have also been associated with a lower risk of dementia in observational studies,[67] this may limit the contrast between the intervention and control group. A different option would be to select another AHM class as control condition, such as angiotensin converting enzyme (ACE) inhibitors, as these are the recommended second choice AHM class and have comparable effectiveness in preventing cardiovascular events.[106,234] Even though, the preDIVA and HATICE trial both assessed the efficacy of a multi-domain intervention targeting multiple cardiovascular risk factors, I would propose to restrict this intervention to this single-domain. The rationale behind a multi-domain intervention is that dementia is a multi-factorial disorder, lifestyle interventions for the different cardiovascular risk factors largely overlap, and the different components might have synergistic effects. The proposed CCB trial is, however, not a lifestyle intervention and there are no theoretical grounds that indicate a synergistic effect. With a single-domain intervention we will be able to draw firm conclusions on the presence of a class-effect and not have a 'black box' problem of not knowing what part of the intervention was effective.

With regard to the choice of the target population, I would recommend to stay as close to clinical practice as possible. In this case that would be to include both people who use AHM and for whom addition of a new antihypertensive drug is indicated, as well as people who have an indication to start AHM. This could be people with or without a history of CVD as, on

the one hand, selection of a high-risk group in a dementia prevention trial is recommended, but on the other hand our subgroup analyses in **chapter three** showed more benefit of CCBs in people without a history of CVD. The exact age range to apply as inclusion criteria is arbitrary. Most AHM class evidence is available for older people,[58] although any intervention effect will probably decrease with increasing age.[28] For optimal comparison, it may be rational to align the age range of this CCB trial to the range used in the preDIVA trial (70-78 years), as this is the population were we found our association with CCBs (**chapter three**). A somewhat younger population (65-75 years) may also be appropriate as we assessed AHM classes in participants who probably already used their AHM for several years. The only exclusion criteria for the trial would be the presence of dementia or another disorder likely to hinder successful follow-up. As GPs prescribe the vast majority of medication for primary and secondary prevention,[235] recruitment via GP practices would be preferable. Recruitment dependent on the active cooperation of the treating physician is known to be difficult, mainly due to time constraints, and can be facilitated by a study nurse.[236] Recruitment in different countries could be considered to enhance generalizability, although this may be difficult to achieve due to large differences in cross-country primary care systems.

Incident all-cause dementia remains the preferred primary outcome measure for trials aimed at reducing cardiovascular risk to prevent dementia. A minimal follow-up period of five years is probably required to demonstrate any impact on the slow disease process of dementia.[51] If we base a sample calculation on the treatment effect, population age, follow-up duration and lost to follow-up of preDIVA (with 80% power and a significance level of 0.05%) we would have to include approximately 1450 participants. However, if you lower the population age to 65-75 years the required sample size increases to approximately 4300 participants, as mean incidence rates are much lower in this age group (1-3 per 1000 person-years).[73] If such a follow-up length and/or large sample size is not possible, an intermediate outcome measure should be chosen. Based on this thesis WMH would seem like a useful intermediate outcome for prevention trials. However, as the causal pathway of the beneficial effect of CCBs is via cerebral perfusion, production of amyloid β or neurofibrillary tangles, or neuronal cell death, for this CCB trial WMH as intermediate outcome would not make sense.[59] In the ongoing *Nilvadipine in Mild-to-Moderate Alzheimer's disease* (NILVAD) trial the effect of the CCB nilvadipine in patients with mild to moderate Alzheimer's disease on cognition is studied.[237] One of the secondary outcome measures of this trial is cerebral blood flow.[238] This trial will provide information on whether the use of CCBs can influence cerebral blood flow in this population and whether this, in turn, leads to an effect on cognition. Whether this result is then also applicable for older people without Alzheimer's disease, and thus if cerebral blood flow can be used as intermediate outcome measure in a primary prevention setting, needs to be assessed. Likewise a z-score of BP decline (comparable to the composite score used in HATICE) would not be useful, as the

theoretical benefit of CCBs lies beyond their BP lowering capacities. If projected incidence rates for dementia are too low to acquire sufficient power, the clinically most appropriate intermediate outcome would therefore probably be a composite cognitive score.
In summary, based on the knowledge acquired in this thesis, I conclude that an RCT is warranted on the effect of CCB versus any other AHM or ACE-inhibitors on the prevention of dementia (or cognitive decline) in older, primary care patients.

SUMMARY

11

With the projected increase in the number of dementia cases there is an urgent need for prevention. Midlife hypertension is one of the most influential risk factors for dementia for which a widely implemented and effective treatment is available. Blood pressure (BP) management could provide a good tool for prevention, but is not yet proven effective. In addition, the relation between BP in late life and dementia is less clear. This thesis is therefore focused on BP management to prevent dementia. In **part I** I assess the complex relation between BP in late life and dementia and in **part II** I study several methodological issues in dementia prevention trials.

Several chapters in this thesis are based on the following two multi-domain prevention trials. *Prevention of Dementia by Intensive Vascular Care* (preDIVA) is a Dutch randomised controlled trial (RCT) on the preventive effect of intensive vascular care during six to eight years on incident dementia among community-dwelling people aged 70-78 years. *Healthy Ageing Through Internet Counselling in the Elderly* (HATICE) is an RCT on the effect of an interactive internet platform for cardiovascular self-management on the cardiovascular risk profile among people aged 65 years and older with an increased cardiovascular risk.

PART I – BLOOD PRESSURE IN LATE LIFE AND DEMENTIA

In **chapter two** we present the results of a systematic review and meta-analysis on the effect of BP-lowering interventions to prevent incident dementia. We could include nine RCTs with a high level of evidence. Seven of the trials focused on antihypertensive medication (AHM) and two on a lifestyle or combined intervention. Collectively, the RCTs reported on 57682 participants. Among the participants receiving a BP-lowering intervention 1041 (3.6%) got diagnosed with dementia versus 1090 (3.8%) of the control participants, resulting in a risk ratio of 0.93 (95% confidence interval [CI] 0.84-1.02). BP-lowering interventions were also not effective when specifying dementia into the subtypes Alzheimer's disease or vascular dementia. The effect was not influenced by duration of the intervention, age or systolic BP. An important methodological limitation is that only one trial performed a competing risk analysis and we could therefore not reliable assess the influence of competing risk of death on our results.

We investigated whether there might be a class-specific beneficial effect of AHM in **chapter three** among the 1951 preDIVA participants with AHM at baseline. Twenty-six of the 522 (5.1%) participant using calcium channel blockers (CCBs) got diagnosed with dementia, which was significantly lower than the 98 (8.5%) participants that got diagnosed with dementia among those using other AHM classes (hazard ratio [HR] 0.56, 95% CI 0.36-0.87). In addition, the number of participants using angiotensin receptor blockers (ARBs) that got diagnosed with dementia (20 out of 389, 5.1%) was significantly lower (HR 0.60, 95% CI 0.37-0.98). Use of diuretics, angiotensin converting enzyme inhibitors or beta-blockers was not associated with a significantly lower or higher dementia risk. The association with

CCBs was most evident in participants without a history of cardiovascular disease and with uncontrolled hypertension. Systolic BP was not significantly lower in participants using CCBs or ARBs.

In **chapter four** we assessed the association between visit-to-visit BP variability and incident dementia. For this analysis we included preDIVA participants with three to five 2-yearly BP measurements. We could not find an association between visit-to-visit BP variability and all-cause dementia (HR 1.00, 95% CI 0.96-1.05). We did find that participants with the highest BP variability had significantly more decline in Mini-Mental State Examination (MMSE; beta -0.09, 95% CI -0.17 to -0.01). The clinical relevance of this small difference in MMSE is, however, uncertain. A higher visit-to-visit BP variability was also associated with an increased risk of cardiovascular disease (HR 1.07, 95% CI 1.04-1.11).

The guidelines on BP management in older people are limited, as the optimal BP treatment in this population is not yet know. In **chapter five** we studied how Dutch general practitioners (GPs) deal with these indistinct directives by inquiring their routines and considerations on prescribing and deprescribing of AHM in older patients. During 15 semi-structured interviews it appeared that GPs have a propensity to continue AHM and that they experience several constraints in starting and stopping or reducing the dosage. This is a consequence of daily routine influenced by time constraints and automated prescription routines. The reluctance in deprescribing AHM was among others influenced by GPs' anticipated regret for a stroke. GPs feel current guidelines provide insufficient guidance.

PART II – METHODOLOGICAL CHALLENGES IN DEMENTIA PREVENTION TRIALS

It is deemed suitable to select people with an increased dementia risk to participate in dementia prevention trials. The best tool to select such an at risk population is, however, unclear. In **chapter six** we assess whether a modifiable dementia risk score is a useful selection tool, by studying whether stratifying the preDIVA study population on *LIfestyle for BRAin health* (LIBRA) index at baseline selects those susceptible to the intervention. Our study showed that the intervention was not more effective in preventing dementia among people with a low (HR 0.71, 95% CI 0.45-1.12), intermediate (HR 1.06, 95% CI 0.66-1.69) or high (HR 1.02, 95% CI 0.64-1.62) LIBRA index. This did not improve when including the non-modifiable risk factors age, education and sex to the LIBRA index. The intervention was also not effective in preventing cognitive decline in people with a low, intermediate or high modifiable dementia risk.

In **chapter seven** we explored the reasons for participating in HATICE. With a mixed-method approach we combined quantitative data from online questionnaires with qualitative data from semi-structured interviews. Participants indicated their main motives for participation were wanting to benefit science, wanting to improve one's lifestyle and benefiting from

additional medical monitoring. Interesting cross-country differences became apparent influenced by societal and healthcare differences. The underlying motivation to participate was preventing dependency.

Long-term adherence to lifestyle changes is difficult to attain and is crucial for cardiovascular prevention. In **chapter eight** we present results of a qualitative study among Dutch intervention participants of the HATICE trial. During 17 semi-structured interviews we have explored older people's experiences with initial and sustained use of the HATICE platform. Participants indicated that human support of their coach was crucial for initial and sustained engagement. Regular automatic and personal reminders also facilitated platform use, however it is unclear whether this also leads to sustained self-management. Increased tailoring of the platform to personal preference could further facilitate engagement. Implementation of such an eHealth intervention is likely most successful if incorporated in the existing cardiovascular prevention programs in primary care.

Cerebral small vessel disease (SVD) has been proposed as intermediate outcome measure in dementia prevention trials, as it is a mediator in the causal pathway between hypertension and dementia. Cerebral SVD is an aggregate term for the neuroradiological markers white matter hyperintensities (WMH), lacunes, microbleeds, enlarged perivascular spaces, acute small subcortical infarcts and brain atrophy. To assess whether AHM can prevent (progression of) cerebral SVD we performed a systematic review and meta-analysis (**chapter nine**). Four trials including 1369 participants found a significantly beneficial effect of AHM on the progression of WMH (standardised mean difference -0.19; 95% CI -0.32 to -0.06). The two trials that assessed the effect of AHM on brain atrophy found no consistent effect (standardised mean difference -0.04; 95% CI -0.66 to 0.58). None of the trials reported on the other SVD markers. WMH progression might be a useful intermediate outcome for dementia prevention trials. However, before WMH can reliable be used as outcome measure, an effect on relevant clinical outcomes should be established.

CONCLUSION

The studies in this thesis have shown that BP-lowering interventions, with AHM and/or lifestyle changes, do not significantly reduce the risk of dementia. Specific classes of AHM (namely, calcium channel blockers and angiotensin receptor blockers) are associated with a lower risk of dementia. A high BP variability is not associated with an increased risk of dementia. Dutch GPs have a tendency to continue AHM and are reluctant in starting and deprescribing. There are many methodological challenges in dementia prevention trials. We have shown that selecting participants based on a modifiable dementia risk score may not be useful. For long-term adherence to an eHealth lifestyle intervention, human support by a coach is crucial. AHM can effectively prevent progression of WMH, a marker of cerebral SVD.

NEDERLANDSE SAMENVATTING

DUTCH SUMMARY

12

Preventie van dementie, ook wel het vóórkomen van dementie, is urgent door de verwachte toename in het aantal mensen met dementie. Hypertensie (een te hoge bloeddruk) op middelbare leeftijd is een van de belangrijkste risicofactoren voor dementie, waarvoor een effectieve en wereldwijd toepasbare behandeling beschikbaar is. Bloeddruk behandeling zou dan ook een geschikte manier kunnen zijn voor de preventie van dementie, maar dit is nog niet bewezen. Daarnaast is de relatie tussen bloeddruk op oudere leeftijd en dementie minder duidelijk. Dit proefschrift gaat over bloeddruk behandeling ter preventie van dementie. In **deel I** heb ik me gericht op de complexe relatie tussen bloeddruk op oudere leeftijd en dementie en in **deel II** op verschillende methodologische problemen in dementie preventie onderzoek.

Enkele hoofdstukken in dit proefschrift zijn gebaseerd op de wetenschappelijke onderzoeken PreDIVA ("*Prevention of Dementia by Intensive Vascular Care*") en HATICE (*"Healthy Ageing Through Internet Counselling in the Elderly"*). Voor deze onderzoeken worden deelnemers gerandomiseerd (geloot) tot een groep waarbij risicofactoren op hart- en vaatziekten (HVZ), zoals hoge bloeddruk en overgewicht, verbeterd worden of tot een controle groep die deze behandeling niet krijgt. PreDIVA is een Nederlands onderzoek onder mensen tussen 70 en 78 jaar waar de behandeling bestaat uit een bezoek aan een praktijkondersteuner elke drie maanden. Na zes tot acht jaar is er gekeken of er in de behandelde groep minder deelnemers dement zijn geworden. HATICE is een onderzoek in Finland, Frankrijk en Nederland waar de behandeling het gebruik van een interactief internet platform is met als doel het verbeteren van de leefstijl gedurende 1,5 jaar.

DEEL I – BLOEDDRUK OP OUDERE LEEFTIJD EN DEMENTIE

In **hoofdstuk twee** beschrijven we een systematische review en meta-analyse naar het effect van bloeddruk verlagende behandeling ter preventie van dementie. Hiervoor konden negen gerandomiseerde onderzoeken meegenomen worden in de analyses. Zeven onderzoeken keken naar het effect van bloeddruk verlagende medicatie (ook wel antihypertensiva genoemd) en twee naar een leefstijl of gecombineerde behandeling. De negen onderzoeken tezamen hadden bijna 58 duizend deelnemers. In de groep deelnemers die de bloeddruk verlagende behandeling kreeg werd 3.6% dement en van de controle groep 3.8%. Dit verschil was niet statistisch significant, en kan dus op kans berusten. Ook zagen we geen effect van bloeddruk verlagende behandeling op de specifieke subtypen van dementie, de ziekte van Alzheimer of vasculaire dementie. Het effect werd niet beïnvloed door de duur van het onderzoek, leeftijd van de deelnemers of hoogte van de bloeddruk. Een belangrijk methodologisch bezwaar van de meta-analyse is dat we geen rekening hebben kunnen houden met het concurrerend risico op overlijden. Bloeddruk verlagende behandeling kan immers het risico op overlijden verlagen, maar daardoor zijn er in die groep wel meer mensen in leven die dement kunnen worden.

In **hoofdstuk drie** hebben we bekeken of het op het dementie risico uitmaakt welk soort antihypertensivum iemand krijgt. De meeste antihypertensiva vallen binnen één van de volgende vijf klassen: diuretica, β-blokkers, calcium antagonisten, ACE-remmers en angiotensine receptor blokkers. Deze onderzoeksvraag hebben we onderzocht onder 1951 preDIVA deelnemers met antihypertensiva. Van de 522 deelnemers met calcium antagonisten kreeg 5% dementie, terwijl dit 8% was onder de deelnemers met een ander type antihypertensivum. Dit verschil was statistisch significant. Het percentage mensen met dementie was ook significant lager onder de 389 deelnemers die angiotensine receptor blokkers gebruikten (5%). De associatie met calcium antagonisten was het sterkste onder deelnemers zonder voorgeschiedenis HVZ en met niet goed gecontroleerde hypertensie. De gemiddelde bloeddruk van deelnemers met calcium antagonisten of angiotensine receptor blokkers was gelijk aan de bloeddruk van deelnemers met een ander antihypertensivum.
In **hoofdstuk vier** hebben we bekeken of het risico op dementie hoger is onder mensen met veel wisselingen in bloeddruk, wat ook wel bloeddruk variabiliteit wordt genoemd. Deze vraag hebben we bekeken onder preDIVA deelnemers met drie tot vijf 2-jaarlijkse bloeddruk metingen. Binnen deze groep konden we geen verband tussen bloeddruk variabiliteit en dementie vinden. We vonden wel dat mensen met een hoge bloeddruk variabiliteit een sterkere afname in cognitie (geheugen, denken etc.) hadden. Dit was echter maar een klein verschil op een vrij grove test. Het is dan ook de vraag of dit significante verschil ook relevant is voor het individu. Er was een verband tussen een hogere bloeddruk variabiliteit een hoger risico op HVZ.
De richtlijnen voor bloeddruk behandeling van ouderen zijn beperkt, omdat het nog niet bekend is hoe je deze groep het beste kan behandelen. In **hoofdstuk vijf** onderzochten we hoe Nederlandse huisartsen met deze onduidelijkheid omgaan in de dagelijkse praktijk door ze te vragen naar hun routines en overwegingen bij het voorschrijven van antihypertensiva. Met behulp van 15 interviews werd duidelijk dat huisartsen een neiging hebben om antihypertensiva voor te blijven schrijven en dat ze terughoudend zijn in het starten en afbouwen of stoppen. Dit is een gevolg van de dagelijkse routine met beperkte tijd en geautomatiseerde voorschrijf routines. De terughoudendheid in het afbouwen van antihypertensiva werd onder andere beïnvloed door verwachte spijt voor het 'veroorzaken' van een beroerte door medicatie af te bouwen. Huisartsen voelen zich onvoldoende gesteund door de huidige richtlijnen.

DEEL II – METHODOLOGISCHE UITDAGINGEN IN DEMENTIE PREVENTIE ONDERZOEK

Voor een gerandomiseerd onderzoek naar de preventie van dementie is het nuttig om deelnemers te selecteren met een verhoogd risico op dementie. Het is alleen nog niet bekend wat voor selectiemiddel hiervoor het meest geschikt is. In **hoofdstuk zes** hebben we bekeken of een dementie risico score op basis van modificeerbare risicofactoren (risicofactoren waar we iets aan kunnen doen) een goed selectiemiddel is. Hiervoor hebben we preDIVA deelnemers in drie groepen verdeeld; deelnemers met een laag, gemiddeld en hoog risico op dementie. Het effect van intensieve vaatzorg op de preventie van dementie verschilde niet in de drie groepen. Het leek zelfs zo dat de vaatzorg effectiever was in de laag risico groep, al was dat verschil niet significant. Het maakte hierbij niet uit of de risicoscore alleen modificeerbare risicofactoren bevatte of ook de niet-modificeerbare risicofactoren leeftijd, geslacht en opleidingsniveau. Intensieve vaatzorg was ook niet effectief in het vóórkomen van cognitieve achteruitgang in de drie groepen.

In **hoofdstuk zeven** hebben we de redenen voor deelname aan HATICE onderzocht. Hiervoor hebben we resultaten van online vragenlijsten gecombineerd met interviews onder Finse, Franse en Nederlandse HATICE deelnemers. De deelnemers gaven aan dat een bijdrage aan wetenschappelijk onderzoek, de wens om hun leefstijl te verbeteren en aanvullende medische monitoring belangrijke redenen waren om mee te doen aan het onderzoek. Verschillen tussen de drie landen werden beïnvloed door maatschappelijk verschillen en verschillen in gezondheidszorg. Een onderliggende motivator voor deelname was vermijden dat ze afhankelijkheid zouden worden van anderen.

Eén van de grootste uitdagingen van behandelingen ter verbetering van de leefstijl is het langdurig volhouden van een goede leefstijl. In **hoofdstuk acht** presenteren we de resultaten van een interviewonderzoek onder Nederlandse HATICE deelnemers die het interactieve platform gebruikten. Tijdens 17 interviews hebben we deelnemers gevraagd naar hun ervaringen met het internet platform en wat voor hen het platform gebruik stimuleerde of beperkte. De deelnemers gaven aan dat met name de ondersteuning door de coach cruciaal was voor verbintenis aan het platform, zowel aan het begin van het onderzoek als op langere termijn. Ook regelmatige automatische en persoonlijke berichten ondersteunden het platformgebruik. Het is alleen onduidelijk of dit ook tot een verbetering van leefstijl kan leiden. Het platform zou kunnen verbeteren door het nog beter aan te passen aan individuele wensen. Deelnemers dachten dat het platform de meeste kans van slagen had als het opgenomen zou worden in de huidige preventie programma's in de huisartspraktijk.

Onderzoek naar de preventie van dementie wordt bemoeilijkt doordat het enkele jaren duurt voordat dementie zich ontwikkelt en het dus lang duurt voordat je weet of een

behandeling effectief is. Een goede vroege uitkomstmaat zou schade aan de kleine vaten in de hersenen (in het Engels 'cerebral small vessel disease') kunnen zijn. Die schade kan je zien op een scan van de hersenen door witte stof afwijkingen, kleine herseninfarcten en bloedingen, en afname van het hersenvolume. In **hoofdstuk negen** hebben we door middel van een systematische review en meta-analyse gekeken of antihypertensiva toename van dit soort schade kan vóórkomen. Vier gerandomiseerde onderzoeken met meer dan duizend deelnemers hebben hier naar gekeken en konden we in onze meta-analyse meenemen. De onderzoeken lieten zien dat het gebruik van antihypertensiva de toename van witte stof afwijkingen kan vóórkomen. De twee onderzoeken die naar afname in hersenvolume hadden gekeken konden echter geen effect van antihypertensiva vinden. De andere kenmerken van schade aan de kleine vaten waren niet onderzocht. Voordat witte stof afwijkingen als vroegtijdige uitkomstmaat voor dementie preventie onderzoek gebruikt kan worden, moet echter wel aangetoond worden dat het preventieve effect op witte stof afwijkingen ook leidt tot een effect op dementie.

CONCLUSIE

De onderzoeken in dit proefschrift hebben laten zien dat bloeddruk behandeling, door middel van medicatie en/of leefstijlverandering, het risico op dementie niet verlaagt. Wel zijn specifieke klassen antihypertensiva (calcium antagonisten en angiotensine receptor blokkers) geassocieerd met een lager risico op dementie. Bloeddruk variabiliteit is niet geassocieerd met een hoger risico op dementie. Huisartsen hebben de neiging antihypertensiva door te blijven schrijven in plaats van de afweging te maken om ze af te bouwen. Er zijn verschillende uitdagingen in het doen van dementie preventie onderzoek. We hebben laten zien dat het selecteren van deelnemers op basis van een dementie risicoscore met modificeerbare risicofactoren niet effectief is. Voor langdurige motivatie voor een leefstijlbehandeling via het internet is ondersteuning door een coach cruciaal. Antihypertensiva zijn effectief in het vóórkomen van toename in witte stof afwijkingen, een kenmerk van schade aan kleine vaten in de hersenen.

APPENDICES

- References
- List of abbreviations
- List of contributing authors
- Data management statement
- List of publications
- PhD portfolio
- Curriculum Vitae
- Acknowledgements (Dankwoord)
- Donders Graduate School for Cognitive Neuroscience
- Dissertations of the disorders of movement research group, Nijmegen

REFERENCES

1. Prince M, Guerchet M, Prina M. Policy brief for heads of government. The global impact of dementia 2013-2050. 2013.
2. World Health Organisation. World report on ageing and health. 2015.
3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 2000.
4. van de Vorst IE, Vaartjes I, Geerlings MI, Bots ML, Koek HL. Prognosis of patients with dementia: results from a prospective nationwide registry linkage study in the Netherlands. *BMJ Open.* 2015;5(10):e008897.
5. World Alzheimer Report 2015. The global impact of dementia. 2015.
6. Jansen D, Werkman W, Francke AL. Dementiemonitor Mantelzorg 2016. Mantelzorgers over zorgbelasting en ondersteuning. 2016.
7. Health Do. G8 dementia summit: Global action against dementia - 11 December 2013. 2014. https://www.gov.uk/government/publications/g8-dementia-summit-global-action-against-dementia/g8-dementia-summit-global-action-against-dementia-11-december-2013. Accessed 14-12-2017.
8. Savva GM, Wharton SB, Ince PG, et al. Age, neuropathology, and dementia. *N Engl J Med.* 2009;360(22):2302-2309.
9. Attems J, Jellinger KA. The overlap between vascular disease and Alzheimer's disease--lessons from pathology. *BMC Med.* 2014;12:206.
10. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol.* 2014;13(8):788-794.
11. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *The Lancet.* 2017;390(10113):2673-2734.
12. Deckers K, van Boxtel MP, Schiepers OJ, et al. Target risk factors for dementia prevention: a systematic review and Delphi consensus study on the evidence from observational studies. *Int J Geriatr Psychiatry.* 2015;30(3):234-246.
13. Ligthart SA, Moll van Charante EP, Van Gool WA, Richard E. Treatment of cardiovascular risk factors to prevent cognitive decline and dementia: a systematic review. *Vasc Health Risk Manag.* 2010;6:775-785.
14. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet.* 2015;385(9984):2255-2263.
15. Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol.* 2017;16(5):377-389.
16. Moll van Charante EP, Richard E, Eurelings LS, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet.* 2016.
17. Richard E, Jongstra S, Soininen H, et al. Healthy Ageing Through Internet Counselling in the Elderly: the HATICE randomised controlled trial for the prevention of cardiovascular disease and cognitive impairment. *BMJ Open.* 2016;6(6):e010806.
18. Jongstra S, Beishuizen C, Andrieu S, et al. Development and Validation of an Interactive Internet Platform for Older People: The Healthy Ageing Through Internet Counselling in the Elderly Study. *Telemed J E Health.* 2016.
19. Iadecola C. Hypertension and dementia. *Hypertension.* 2014;64(1):3-5.
20. Ruitenberg A, Skoog I, Ott A, et al. Blood pressure and risk of dementia: results from the Rotterdam study and the Gothenburg H-70 Study. *Dement Geriatr Cogn Disord.* 2001;12(1):33-39.
21. Peters R, Beckett N, Forette F, et al. Incident dementia and blood pressure lowering in the Hypertension in the Very Elderly Trial cognitive function assessment (HYVET-COG): a double-blind, placebo controlled trial. *Lancet Neurol.* 2008;7(8):683-689.

22. Rouch L, Cestac P, Hanon O, et al. Antihypertensive drugs, prevention of cognitive decline and dementia: a systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. *CNS Drugs*. 2015;29(2):113-130.
23. Jongstra S, Harrison JK, Quinn TJ, Richard E. Antihypertensive withdrawal for the prevention of cognitive decline. *Cochrane Database Syst Rev*. 2016;11:CD011971.
24. Moonen JE, Foster-Dingley JC, de Ruijter W, et al. Effect of Discontinuation of Antihypertensive Treatment in Elderly People on Cognitive Functioning--the DANTE Study Leiden: A Randomized Clinical Trial. *JAMA Intern Med*. 2015;175(10):1622-1630.
25. McGrath ER, Beiser AS, DeCarli C, et al. Blood pressure from mid- to late life and risk of incident dementia. *Neurology*. 2017;89(24):2447-2454.
26. Nagai M, Dote K, Kato M, et al. Visit-to-Visit Blood Pressure Variability and Alzheimer's Disease: Links and Risks. *J Alzheimers Dis*. 2017.
27. Muntner P, Whittle J, Lynch AI, et al. Visit-to-Visit Variability of Blood Pressure and Coronary Heart Disease, Stroke, Heart Failure, and Mortality: A Cohort Study. *Ann Intern Med*. 2015;163(5):329-338.
28. Richard E, Andrieu S, Solomon A, et al. Methodological challenges in designing dementia prevention trials - the European Dementia Prevention Initiative (EDPI). *J Neurol Sci*. 2012;322(1-2):64-70.
29. Mellen PB, Gao SK, Vitolins MZ, Goff DC, Jr. Deteriorating dietary habits among adults with hypertension: DASH dietary accordance, NHANES 1988-1994 and 1999-2004. *Arch Intern Med*. 2008;168(3):308-314.
30. Patel B, Markus HS. Magnetic resonance imaging in cerebral small vessel disease and its use as a surrogate disease marker. *Int J Stroke*. 2011;6(1):47-59.
31. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European heart journal*. 2016;37(29):2315-2381.
32. Boubouchairopoulou N, Karpettas N, Athanasakis K, et al. Cost estimation of hypertension management based on home blood pressure monitoring alone or combined office and ambulatory blood pressure measurements. *J Am Soc Hypertens*. 2014;8(10):732-738.
33. McGuinness B, Todd S, Passmore P, Bullock R. Blood pressure lowering in patients without prior cerebrovascular disease for prevention of cognitive impairment and dementia. *Cochrane Database Syst Rev*. 2009(4):CD004034.
34. Sisti LG, Dajko M, Campanella P, Shkurti E, Ricciardi W, de Waure C. The effect of multifactorial lifestyle interventions on cardiovascular risk factors: A systematic review and meta-analysis of trials conducted in the general population and high risk groups. *Prev Med*. 2017.
35. Espeland MA, Luchsinger JA, Baker LD, et al. Effect of a long-term intensive lifestyle intervention on prevalence of cognitive impairment. *Neurology*. 2017;88(21):2026-2035.
36. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4:1.
37. Van Middelaar T, Van Vught LA, Van Gool WA, Van den Born BH, Moll van Charante EP, Richard E. The effectiveness of antihypertensive treatment in preventing incident dementia; a systematic review and meta-analysis. 2017. CRD42017056875. http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017056875.
38. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
39. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
40. J. P. T. Higgins, S. Green. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. . 2011: www.handbook.cochrane.org.
41. van Middelaar T, van Vught LA, Moll van Charante EP, et al. Lower dementia risk with different classes of antihypertensive medication in older patients. *Journal of hypertension*. 2017.

42. R Core Team. R: A language and environment for statistical computing. 2016: https://www.R-project.org/.
43. Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA.* 1996;276(23):1886-1892.
44. Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment: new evidence from the Systolic Hypertension in Europe (Syst-Eur) study. *Arch Intern Med.* 2002;162(18):2046-2052.
45. Lithell H, Hansson L, Skoog I, et al. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *Journal of hypertension.* 2003;21(5):875-886.
46. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med.* 2003;163(9):1069-1075.
47. Patel A, Group AC, MacMahon S, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet.* 2007;370(9590):829-840.
48. Diener HC, Sacco RL, Yusuf S, et al. Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study. *Lancet Neurol.* 2008;7(10):875-884.
49. Anderson C, Teo K, Gao P, et al. Renin-angiotensin system blockade and cognitive function in patients at high risk of cardiovascular disease: analysis of data from the ONTARGET and TRANSCEND studies. *Lancet Neurol.* 2011;10(1):43-53.
50. Wright JT, Jr., Whelton PK, Reboussin DM. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med.* 2016;374(23):2294.
51. Skoog I. Antihypertensive treatment and dementia prevention. *Lancet Neurol.* 2008;7(8):664-665.
52. Austin PC, Fine JP. Accounting for competing risks in randomized controlled trials: a review and recommendations for improvement. *Statistics in Medicine.* 2017;36(8):1203-1209.
53. Matthews F, Brayne C. The incidence of dementia in England and Wales: findings from the five identical sites of the MRC CFA Study. *PLoS Med.* 2005;2(8):e193.
54. Yusuf S, Diener HC, Sacco RL, et al. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med.* 2008;359(12):1225-1237.
55. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet.* 2001;358(9287):1033-1041.
56. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement.* 2013;9(1):63-75 e62.
57. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Journal of hypertension.* 2013;31(7):1281-1357.
58. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. *Journal of hypertension.* 2013;31(6):1073-1082.
59. Peters R, Schuchman M, Peters J, Carlson MC, Yasar S. Relationship Between Antihypertensive Medications and Cognitive Impairment: Part II. Review of Physiology and Animal Studies. *Curr Hypertens Rep.* 2016;18(8):66.
60. Shah K, Qureshi SU, Johnson M, Parikh N, Schulz PE, Kunik ME. Does use of antihypertensive drugs affect the incidence or progression of dementia? A systematic review. *Am J Geriatr Pharmacother.* 2009;7(5):250-261.
61. van Charante EP, Richard E, Eurelings LS, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet (London, England).* 2016.
62. Richard E, Van den Heuvel E, Moll van Charante EP, et al. Prevention of dementia by intensive vascular care (PreDIVA): a cluster-randomized trial in progress. *Alzheimer Dis Assoc Disord.* 2009;23(3):198-204.

63. World Health Organization. Global Recommendations on Physical Activity for Health. 2010: http://apps.who.int/iris/bitstream/10665/44399/1/9789241599979_eng.pdf.
64. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12(3):189-198.
65. Burgers JS, Simoons ML, Hoes AW, Stehouwer CD, Stalman WA. [Guideline 'Cardiovascular Risk Management']. *Ned Tijdschr Geneeskd.* 2007;151(19):1068-1074.
66. Bellera CA, MacGrogan G, Debled M, de Lara CT, Brouste V, Mathoulin-Pelissier S. Variables with time-varying effects and the Cox model: some statistical concepts illustrated with a prognostic factor study in breast cancer. *BMC Med Res Methodol.* 2010;10:20.
67. Tully PJ, Dartigues JF, Debette S, Helmer C, Artero S, Tzourio C. Dementia risk with antihypertensive use and blood pressure variability: A cohort study. *Neurology.* 2016.
68. Bradford A, Kunik ME, Schulz P, Williams SP, Singh H. Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. *Alzheimer Dis Assoc Disord.* 2009;23(4):306-314.
69. Hinchliffe SR, Lambert PC. Flexible parametric modelling of cause-specific hazards to estimate cumulative incidence functions. *BMC Med Res Methodol.* 2013;13:13.
70. Nimmrich V, Eckert A. Calcium channel blockers and dementia. *Br J Pharmacol.* 2013;169(6):1203-1210.
71. Peters R, Booth A, Peters J. A systematic review of calcium channel blocker use and cognitive decline/dementia in the elderly. *Journal of hypertension.* 2014;32(10):1945-1957; discussion 1957-1948.
72. Ligthart SA, Richard E, van Gool WA, Moll van Charante EP. Cardiovascular risk management in community-dwelling elderly: opportunities for prevention. *Eur J Prev Cardiol.* 2012;19(6):1365-1372.
73. van Bussel EF, Richard E, Arts DL, et al. Dementia incidence trend over 1992-2014 in the Netherlands: Analysis of primary care data. *PLoS Med.* 2017;14(3):e1002235.
74. Qiu CX, Winblad B, Fratiglioni L. The age-dependent relation of blood pressure to cognitive function and dementia. *Lancet Neurology.* 2005;4(8):487-499.
75. Stewart R, Xue QL, Masaki K, et al. Change in Blood Pressure and Incident Dementia A 32-Year Prospective Study. *Hypertension.* 2009;54(2):233-240.
76. Rothwell PM. Limitations of the usual blood-pressure hypothesis and importance of variability, instability, and episodic hypertension. *Lancet.* 2010;375(9718):938-948.
77. Sabayan B, Wijsman LW, Foster-Dingley JC, et al. Association of visit-to-visit variability in blood pressure with cognitive function in old age: prospective cohort study. *BMJ.* 2013;347:f4600.
78. Alperovitch A, Blachier M, Soumare A, et al. Blood pressure variability and risk of dementia in an elderly cohort, the Three-City Study. *Alzheimers Dement.* 2014;10(5 Suppl):S330-337.
79. Brickman AM, Reitz C, Luchsinger JA, et al. Long-term blood pressure fluctuation and cerebrovascular disease in an elderly cohort. *Arch Neurol.* 2010;67(5):564-569.
80. Altunkan S, Iliman N, Altunkan E. Validation of the Omron M6 (HEM-7001-E) upper arm blood pressure measuring device according to the International Protocol in elderly patients. *Blood Press Monit.* 2008;13(2):117-122.
81. Webb AJ, Fischer U, Rothwell PM. Effects of beta-blocker selectivity on blood pressure variability and stroke: a systematic review. *Neurology.* 2011;77(8):731-737.
82. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet.* 2010;375(9718):895-905.
83. Poortvliet RKE, de Ruijter W, de Craen AJM, et al. Blood pressure trends and mortality: the Leiden 85-plus Study. *Journal of hypertension.* 2013;31(1):63-70.
84. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. *Nat Rev Cardiol.* 2013;10(3):143-155.
85. Hughes TM, Kuller LH, Barinas-Mitchell EJ, et al. Pulse wave velocity is associated with beta-amyloid deposition in the brains of very elderly adults. *Neurology.* 2013;81(19):1711-1718.

86. Nagai M, Hoshide S, Ishikawa J, Shimada K, Kario K. Visit-to-visit blood pressure variations: new independent determinants for cognitive function in the elderly at high risk of cardiovascular disease. *Journal of hypertension*. 2012;30(8):1556-1563.
87. Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis. *Lancet*. 2010;375(9718):906-915.
88. Bates D, Machler M, Bolker BM, Walker SC. Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*. 2015;67(1):1-48.
89. Therneau T. A Package for Survival Analysis in S. 2015; https://CRAN.R-project.org/package=survival.
90. Gu A, Yue Y, Argulian E. Age Differences in Treatment and Control of Hypertension in US Physician Offices, 2003-2010: A Serial Cross-sectional Study. *Am J Med*. 2016;129(1):50-58 e54.
91. Streit S, Verschoor M, Rodondi N, et al. Variation in GP decisions on antihypertensive treatment in oldest-old and frail individuals across 29 countries. *BMC Geriatr*. 2017;17(1):93.
92. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, et al. Treatment of hypertension in patients 80 years and older: the lower the better? A meta-analysis of randomized controlled trials. *Journal of hypertension*. 2010;28(7):1366-1372.
93. Group SR, Wright JT, Jr., Williamson JD, et al. *A Randomized Trial of Intensive versus Standard Blood-Pressure Control*. Vol 373: N Engl J Med; 2015.
94. Williamson JD, Supiano MA, Applegate WB, et al. Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged >/=75 Years: A Randomized Clinical Trial. *JAMA*. 2016;315(24):2673-2682.
95. Marcum ZA, Perera S, Newman AB, et al. Antihypertensive Use and Recurrent Falls in Community-Dwelling Older Adults: Findings From the Health ABC Study. *J Gerontol A Biol Sci Med Sci*. 2015;70(12):1562-1568.
96. Supiano MA, Williamson JD. Applying the Systolic Blood Pressure Intervention Trial Results to Older Adults. *J Am Geriatr Soc*. 2017;65(1):16-21.
97. Chobanian AV. SPRINT Results in Older Patients: How Low to Go? *JAMA*. 2016;315(24):2669-2670.
98. Muller M, Smulders YM, de Leeuw PW, Stehouwer CD. Treatment of hypertension in the oldest old: a critical role for frailty? *Hypertension*. 2014;63(3):433-441.
99. Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA*. 2000;284(3):357-362.
100. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006;3(2):77-101.
101. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing*. 2015;44(2):213-218.
102. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care*. 2007;19(6):349-357.
103. Schafer WL, Boerma WG, Spreeuwenberg P, Schellevis FG, Groenewegen PP. Two decades of change in European general practice service profiles: conditions associated with the developments in 28 countries between 1993 and 2012. *Scand J Prim Health Care*. 2016;34(1):97-110.
104. van den Berg MJ, van Loenen T, Westert GP. Accessible and continuous primary care may help reduce rates of emergency department use. An international survey in 34 countries. *Fam Pract*. 2016;33(1):42-50.
105. Ohlsson H, Vervloet M, van Dijk L. Practice variation in a longitudinal perspective: a multilevel analysis of the prescription of simvastatin in general practices between 2003 and 2009. *European journal of clinical pharmacology*. 2011;67(12):1205-1211.
106. Wiersma T, Smulders YM, Stehouwer CD, Konings KT, Lanphen J. [Summary of the multidisciplinary guideline on cardiovascular risk management (revision 2011)]. *Ned Tijdschr Geneeskd*. 2012;156(36):A5104.
107. Voogdt-Pruis HR, Van Ree JW, Gorgels AP, Beusmans GH. Adherence to a guideline on cardiovascular prevention: a comparison between general practitioners and practice nurses. *Int J Nurs Stud*. 2011;48(7):798-807.

108. Drewes YM, Koenen JM, de Ruijter W, et al. GPs' perspectives on preventive care for older people: a focus group study. *Br J Gen Pract.* 2012;62(604):e765-772.
109. van Peet PG, Drewes YM, Gussekloo J, de Ruijter W. GPs' perspectives on secondary cardiovascular prevention in older age: a focus group study in the Netherlands. *Br J Gen Pract.* 2015;65(640):e739-747.
110. Jansen J, McKinn S, Bonner C, et al. General Practitioners' Decision Making about Primary Prevention of Cardiovascular Disease in Older Adults: A Qualitative Study. *PLoS One.* 2017;12(1):e0170228.
111. van Summeren JJ, Schuling J, Haaijer-Ruskamp FM, Denig P. Outcome prioritisation tool for medication review in older patients with multimorbidity: a pilot study in general practice. *Br J Gen Pract.* 2017;67(660):e501-e506.
112. Mermans E, Degryse J, Vaes B. Treatment intentions of general practitioners regarding hypertension in the oldest old: a vignette study. *BMC Fam Pract.* 2016;17(1):122.
113. Jansen J, Naganathan V, Carter SM, et al. Too much medicine in older people? Deprescribing through shared decision making. *Bmj.* 2016;353:i2893.
114. Luymes CH, Boelhouwer NH, Poortvliet RKE, De Ruijter W, Reis R, Numans ME. Understanding deprescribing of preventive cardiovascular medication: a Q-methodology study in patients. *Patient Preference and Adherence.* 2017;11:975-984.
115. Weir K, Nickel B, Naganathan V, et al. Decision-Making Preferences and Deprescribing: Perspectives of Older Adults and Companions About Their Medicines. *The journals of gerontology Series B, Psychological sciences and social sciences.* 2017.
116. Schuling J, Gebben H, Veehof LJ, Haaijer-Ruskamp FM. Deprescribing medication in very elderly patients with multimorbidity: the view of Dutch GPs. A qualitative study. *BMC Fam Pract.* 2012;13:56.
117. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP, intervention IPSCIDAoA. J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient data. *Ann Intern Med.* 2002;136(6):438-448.
118. Ogliari G, Westendorp RG, Muller M, et al. Blood pressure and 10-year mortality risk in the Milan Geriatrics 75+ Cohort Study: role of functional and cognitive status. *Age Ageing.* 2015;44(6):932-937.
119. Scheltens P, Blennow K, Breteler MMB, et al. Alzheimer's disease. *The Lancet.*388(10043):505-517.
120. Imtiaz B, Tolppanen AM, Kivipelto M, Soininen H. Future directions in Alzheimer's disease from risk factors to prevention. *Biochemical pharmacology.* 2014;88(4):661-670.
121. Schiepers OJ, Kohler S, Deckers K, et al. Lifestyle for Brain Health (LIBRA): a new model for dementia prevention. *Int J Geriatr Psychiatry.* 2017.
122. Vos SJB, van Boxtel MPJ, Schiepers OJG, et al. Modifiable Risk Factors for Prevention of Dementia in Midlife, Late Life and the Oldest-Old: Validation of the LIBRA Index. *J Alzheimers Dis.* 2017;58(2):537-547.
123. Pocklington C, Gilbody S, Manea L, McMillan D. The diagnostic accuracy of brief versions of the Geriatric Depression Scale: a systematic review and meta-analysis. *Int J Geriatr Psychiatry.* 2016;31(8):837-857.
124. Stel VS, Smit JH, Pluijm SM, Visser M, Deeg DJ, Lips P. Comparison of the LASA Physical Activity Questionnaire with a 7-day diary and pedometer. *J Clin Epidemiol.* 2004;57(3):252-258.
125. Kivipelto M, Ngandu T, Laatikainen T, Winblad B, Soininen H, Tuomilehto J. Risk score for the prediction of dementia risk in 20 years among middle aged people: a longitudinal, population-based study. *Lancet Neurol.* 2006;5(9):735-741.
126. Authors/Task Force M, Piepoli MF, Hoes AW, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol.* 2016;23(11):NP1-NP96.
127. Kilbride HS, Stevens PE, Eaglestone G, et al. Accuracy of the MDRD (Modification of Diet in Renal Disease) study and CKD-EPI (CKD Epidemiology Collaboration) equations for estimation of GFR in the elderly. *Am J Kidney Dis.* 2013;61(1):57-66.

128. Lindeboom J, Schmand B, Tulner L, Walstra G, Jonker C. Visual association test to detect early dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry.* 2002;73(2):126-133.
129. Gee KA. Multilevel Growth Modeling:An Introductory Approach to Analyzing Longitudinal Data for Evaluators. *American Journal of Evaluation.* 2014;35(4):543-561.
130. Team RC. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2017.
131. Wilson RS, Barnes LL, Aggarwal NT, et al. Cognitive activity and the cognitive morbidity of Alzheimer disease. *Neurology.* 2010;75(11):990-996.
132. World Health Organization, National Institute on Aging, National Institutes of Health. Global Health and Aging. 2011.
133. Eurostat. Internet access and use statistics - households and individuals. 2016; http://ec.europa.eu/eurostat/statistics-explained/index.php/Internet_access_and_use_statistics_-_households_and_individuals. Accessed 21-2-2018.
134. Cusack S, O'Toole PW, consortium E. Challenges and implications for biomedical research and intervention studies in older populations: insights from the ELDERMET study. *Gerontology.* 2013;59(2):114-121.
135. Fearn P, Avenell A, McCann S, Milne AC, Maclennan G, Mavis Trial G. Factors influencing the participation of older people in clinical trials - data analysis from the MAVIS trial. *J Nutr Health Aging.* 2010;14(1):51-56.
136. McHenry JC, Insel KC, Einstein GO, Vidrine AN, Koerner KM, Morrow DG. Recruitment of Older Adults: Success May Be in the Details. *Gerontologist.* 2015;55(5):845-853.
137. Coley N, Andrieu S. Participation of older people in clinical trials. In: A. Sinclair, J. Pathy, J. Morley, V. Vellas, eds. *Pathy's Principles and Practice of Geriatric Medicine, 5th edition*: John Wiley & Sons, Ltd 2012.
138. Beishuizen CR, Stephan BC, van Gool WA, et al. Web-Based Interventions Targeting Cardiovascular Risk Factors in Middle-Aged and Older People: A Systematic Review and Meta-Analysis. *J Med Internet Res.* 2016;18(3):e55.
139. Andrieu S, Coley N, Gardette V, et al. Representations and practices of prevention in elderly populations: investigating acceptance to participate in and adhesion to an intervention study for the prevention of Alzheimer's disease (ACCEPT study)--the need for a multidisciplinary approach. *J Nutr Health Aging.* 2012;16(4):352-354.
140. Krippendorff K. *Content Analysis. An Introduction to its Methodology.* Los Angeles: Sage; 2004.
141. Fowler JH, Kam CD. Beyond the self: Social identity, altruism, and political participation. *Journal of Politics.* 2007;69(3):813-234.
142. Bolin K, Lindgren B, Lundborg P. Informal and formal care among single-living elderly in Europe. *Health Econ.* 2008;17(3):393-409.
143. Bettio F, Plantenga J. Comparing Care Regimes in Europe. *Feminist Economics.* 2004;10(1):85-113.
144. Drulhe M, Clément S. Transmission du patrimoine et prise en charge des parents âgés du Sud-Ouest rural. *Sociétés contemporaines.* 1992;10(1):93-109.
145. Mallon I. L'accompagnement du vieillissement en milieu rural au-delà de la solidarité intergénérationnelle. *Informations sociales.* 2011(2):100-108.
146. Lakerveld J, Ijzelenberg W, van Tulder MW, et al. Motives for (not) participating in a lifestyle intervention trial. *BMC Med Res Methodol.* 2008;8:17.
147. Nosraty L, Jylha M, Raittila T, Lumme-Sandt K. Perceptions by the oldest old of successful aging, Vitality 90+ Study. *J Aging Stud.* 2015;32:50-58.
148. Ligthart SA, van den Eerenbeemt KD, Pols J, van Bussel EF, Richard E, Moll van Charante EP. Perspectives of older people engaging in nurse-led cardiovascular prevention programmes: a qualitative study in primary care in the Netherlands. *Br J Gen Pract.* 2015;65(630):e41-48.
149. Reed RL, Barton CA, Isherwood LM, Baxter JM, Roeger L. Recruitment for a clinical trial of chronic disease self-management for older adults with multimorbidity: a successful approach within general practice. *BMC Fam Pract.* 2013;14:125.

150. Tolmie EP, Mungall MM, Louden G, Lindsay GM, Gaw A. Understanding why older people participate in clinical trials: the experience of the Scottish PROSPER participants. *Age Ageing.* 2004;33(4):374-378.

151. Raivio R, Jaaskelainen J, Holmberg-Marttila D, Mattila KJ. Decreasing trends in patient satisfaction, accessibility and continuity of care in Finnish primary health care - a 14-year follow-up questionnaire study. *BMC Fam Pract.* 2014;15:98.

152. State of Health in the EU. Finland. Country Health Profile 2017. 2017: http://www.oecd-ilibrary.org/docserver/download/8117461e.pdf?expires=1519401104&id=id&accname=guest&checksum=FAC27E34C4EB80012E90468CB13ED730. Accessed 23-02-3018.

153. Kringos D, Boerma W, Bourgueil Y, et al. The strength of primary care in Europe: an international comparative study. *Br J Gen Pract.* 2013;63(616):e742-750.

154. Special Eurobarometer 411. Patient safety and quality of care. 2014: https://ec.europa.eu/health/sites/health/files/patient_safety/docs/ebs_411_sum_en.pdf. Accessed 23-02-2018.

155. Dangour AD, Allen E, Richards M, Whitehouse P, Uauy R. Design considerations in long-term intervention studies for the prevention of cognitive decline or dementia. *Nutr Rev.* 2010;68 Suppl 1:S16-21.

156. van Middelaar T, Beishuizen CRL, Guillemont J, et al. Engaging older people in an internet platform for cardiovascular risk self-management: a qualitative study among Dutch HATICE participants. *BMJ Open.* 2018;8(1):e019683.

157. Abegunde DO, Mathers CD, Adam T, Ortegon M, Strong K. The burden and costs of chronic diseases in low-income and middle-income countries. *Lancet.* 2007;370(9603):1929-1938.

158. Mons U, Muezzinler A, Gellert C, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. *BMJ.* 2015;350:h1551.

159. Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. *Circulation.* 2010;121(6):750-758.

160. World Health Organization. Adherence to long-term therapies: evidence for action. 2003: http://www.who.int/chp/knowledge/publications/adherence_report/en/. Accessed 17-10-2017.

161. Nouwens E, van Lieshout J, van den Hombergh P, Laurant M, Wensing M. Shifting cardiovascular care to nurses results in structured chronic care. *Am J Manag Care.* 2014;20(7):e278-284.

162. Pagliari C, Sloan D, Gregor P, et al. What is eHealth (4): a scoping exercise to map the field. *J Med Internet Res.* 2005;7(1):e9.

163. Kohl LF, Crutzen R, de Vries NK. Online prevention aimed at lifestyle behaviors: a systematic review of reviews. *J Med Internet Res.* 2013;15(7):e146.

164. O'Connor S, Hanlon P, O'Donnell CA, Garcia S, Glanville J, Mair FS. Understanding factors affecting patient and public engagement and recruitment to digital health interventions: a systematic review of qualitative studies. *BMC medical informatics and decision making.* 2016;16(1):120.

165. Becker SA. A study of web usability for older adults seeking online health resources. *ACM Trans Comput Hum Interact.* 2004;11:387-406.

166. Peters DH, Adam T, Alonge O, Agyepong IA, Tran N. Implementation research: what it is and how to do it. *BMJ.* 2013;347:f6753.

167. Glasgow RE, Phillips SM, Sanchez MA. Implementation science approaches for integrating eHealth research into practice and policy. *Int J Med Inform.* 2014;83(7):e1-11.

168. Bandura A. Health promotion by social cognitive means. *Health education & behavior : the official publication of the Society for Public Health Education.* 2004;31(2):143-164.

169. Michie S, Richardson M, Johnston M, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine.* 2013;46(1):81-95.

170. Rollnick S, Miller WR, Butler CC. Motivational interviewing in health care: helping patients change behavior. New York: The Guilford Press; 2008.
171. Prochaska JO, Diclemente CC, Norcross JC. In Search of How People Change - Applications to Addictive Behaviors. *Am Psychol.* 1992;47(9):1102-1114.
172. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?". *Lancet.* 2005;365(9453):82-93.
173. Shingleton RM, Palfai TP. Technology-delivered adaptations of motivational interviewing for health-related behaviors: A systematic review of the current research. *Patient Educ Couns.* 2016;99(1):17-35.
174. Vervloet M, Linn AJ, van Weert JC, de Bakker DH, Bouvy ML, van Dijk L. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. *J Am Med Inform Assoc.* 2012;19(5):696-704.
175. Schermer M. Telecare and self-management: opportunity to change the paradigm? *Journal of medical ethics.* 2009;35(11):688-691.
176. Eurostat. Internet access and use statistics - households and individuals. http://ec.europa.eu/eurostat/statistics-explained/index.php/Internet_access_and_use_statistics_-_households_and_individuals. Accessed 24-04-2017.
177. Conway N, Webster C, Smith B, Wake D. eHealth and the use of individually tailored information: A systematic review. *Health Informatics J.* 2016.
178. Brown LL, Lustria ML, Rankins J. A review of web-assisted interventions for diabetes management: maximizing the potential for improving health outcomes. *J Diabetes Sci Technol.* 2007;1(6):892-902.
179. Saner H, van der Velde E. eHealth in cardiovascular medicine: A clinical update. *Eur J Prev Cardiol.* 2016;23(2 suppl):5-12.
180. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. *Lancet Neurol.* 2010;9(7):689-701.
181. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol.* 2013;12(8):822-838.
182. Wilson D, Charidimou A, Werring DJ. Advances in understanding spontaneous intracerebral hemorrhage: insights from neuroimaging. *Expert Rev Neurother.* 2014;14(6):661-678.
183. van Leijsen EMC, de Leeuw FE, Tuladhar AM. Disease progression and regression in sporadic small vessel disease-insights from neuroimaging. *Clin Sci (Lond).* 2017;131(12):1191-1206.
184. Staals J, Makin SD, Doubal FN, Dennis MS, Wardlaw JM. Stroke subtype, vascular risk factors, and total MRI brain small-vessel disease burden. *Neurology.* 2014;83(14):1228-1234.
185. Musini VM, Tejani AM, Bassett K, Wright JM. Pharmacotherapy for hypertension in the elderly. *Cochrane Database Syst Rev.* 2009(4):CD000028.
186. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557-560.
187. Higgins JP, White IR, Anzures-Cabrera J. Meta-analysis of skewed data: combining results reported on log-transformed or raw scales. *Stat Med.* 2008;27(29):6072-6092.
188. Weber R, Weimar C, Blatchford J, et al. Telmisartan on top of antihypertensive treatment does not prevent progression of cerebral white matter lesions in the prevention regimen for effectively avoiding second strokes (PRoFESS) MRI substudy. *Stroke; a journal of cerebral circulation.* 2012;43(9):2336-2342.
189. Williamson JD, Launer LJ, Bryan RN, et al. Cognitive function and brain structure in persons with type 2 diabetes mellitus after intensive lowering of blood pressure and lipid levels: a randomized clinical trial. *JAMA Intern Med.* 2014;174(3):324-333.
190. Firbank MJ, Wiseman RM, Burton EJ, Saxby BK, O'Brien JT, Ford GA. Brain atrophy and white matter hyperintensity change in older adults and relationship to blood pressure. Brain atrophy, WMH change and blood pressure. *J Neurol.* 2007;254(6):713-721.

191. Dufouil C, Chalmers J, Coskun O, et al. Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy. *Circulation*. 2005;112(11):1644-1650.
192. Murray AM, Hsu FC, Williamson JD, et al. ACCORDION MIND: results of the observational extension of the ACCORD MIND randomised trial. *Diabetologia*. 2017;60(1):69-80.
193. Erten-Lyons D, Dodge HH, Woltjer R, et al. Neuropathologic basis of age-associated brain atrophy. *JAMA Neurol*. 2013;70(5):616-622.
194. Jochemsen HM, Muller M, Visseren FL, et al. Blood pressure and progression of brain atrophy: the SMART-MR Study. *JAMA Neurol*. 2013;70(8):1046-1053.
195. de la Torre JC. Critically attained threshold of cerebral hypoperfusion: can it cause Alzheimer's disease? *Ann N Y Acad Sci*. 2000;903:424-436.
196. Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ. Low blood pressure and the risk of dementia in very old individuals. *Neurology*. 2003;61(12):1667-1672.
197. Bangalore S, Messerli FH, Wun CC, et al. J-curve revisited: An analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. *European heart journal*. 2010;31(23):2897-2908.
198. van Dijk EJ, Breteler MM, Schmidt R, et al. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. *Hypertension*. 2004;44(5):625-630.
199. Ambrosius WT, Sink KM, Foy CG, et al. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). *Clin Trials*. 2014;11(5):532-546.
200. van Leijsen EMC, van Uden IWM, Ghafoorian M, et al. Nonlinear temporal dynamics of cerebral small vessel disease: The RUN DMC study. *Neurology*. 2017.
201. Zanchetti A. Bottom blood pressure or bottom cardiovascular risk? How far can cardiovascular risk be reduced? *Journal of hypertension*. 2009;27(8):1509-1520.
202. van Dalen JW, Moll van Charante EP, Caan MWA, et al. Effect of Long-Term Vascular Care on Progression of Cerebrovascular Lesions: Magnetic Resonance Imaging Substudy of the PreDIVA Trial (Prevention of Dementia by Intensive Vascular Care). *Stroke; a journal of cerebral circulation*. 2017;48(7):1842-1848.
203. De Guio F, Jouvent E, Biessels GJ, et al. Reproducibility and variability of quantitative magnetic resonance imaging markers in cerebral small vessel disease. *J Cereb Blood Flow Metab*. 2016;36(8):1319-1337.
204. Boller F, Forbes MM. History of dementia and dementia in history: an overview. *J Neurol Sci*. 1998;158(2):125-133.
205. Reed BR. Vascular dementia. *Arch Neurol*. 2004;61(3):433-435.
206. Cipriani G, Dolciotti C, Picchi L, Bonuccelli U. Alzheimer and his disease: a brief history. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2011;32(2):275-279.
207. Rahman F, McEvoy JW. The J-shaped Curve for Blood Pressure and Cardiovascular Disease Risk: Historical Context and Recent Updates. *Current atherosclerosis reports*. 2017;19(8):34.
208. Mahmood SS, Levy D, Vasan RS, Wang TJ. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. *Lancet*. 2014;383(9921):999-1008.
209. Elias MF, Goodell AL, Dore GA. Hypertension and cognitive functioning: a perspective in historical context. *Hypertension*. 2012;60(2):260-268.
210. Hofman A, Ott A, Breteler MM, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. *Lancet*. 1997;349(9046):151-154.
211. Eguchi K. Effects of Antihypertensive Therapy on Blood Pressure Variability. *Curr Hypertens Rep*. 2016;18(10):75.
212. Peters R, Yasar S, Anstey KJ, Booth A. Exposure to antihypertensive classes and their relationship with subsequent cognitive decline/dementia. 2016. http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016045454.

213. Kyriacou DN, Lewis RJ. Confounding by Indication in Clinical Research. *Jama.* 2016;316(17):1818-1819.

214. Hajjar I, Quach L, Yang F, et al. Hypertension, white matter hyperintensities, and concurrent impairments in mobility, cognition, and mood: the Cardiovascular Health Study. *Circulation.* 2011;123(8):858-865.

215. Richard E, Ligthart SA, Moll van Charante EP, van Gool WA. Vascular risk factors and dementia--towards prevention strategies. *Neth J Med.* 2010;68(10):284-290.

216. Hajjar I, Brown L, Mack WJ, Chui H. Impact of Angiotensin receptor blockers on Alzheimer disease neuropathology in a large brain autopsy series. *Arch Neurol.* 2012;69(12):1632-1638.

217. Oishi E, Ohara T, Sakata S, et al. Day-to-Day Blood Pressure Variability and Risk of Dementia in a General Japanese Elderly Population: The Hisayama Study. *Circulation.* 2017;136(6):516-525.

218. Ravindrarajah R, Hazra NC, Hamada S, et al. Systolic Blood Pressure Trajectory, Frailty, and All-Cause Mortality >80 Years of Age: Cohort Study Using Electronic Health Records. *Circulation.* 2017;135(24):2357-2368.

219. Kalkman DN, Brouwer TF, Vehmeijer JT, et al. J Curve in Patients Randomly Assigned to Different Systolic Blood Pressure Targets: An Experimental Approach to an Observational Paradigm. *Circulation.* 2017;136(23):2220-2229.

220. Delgado J, Bowman K, Ble A, et al. Blood Pressure Trajectories in the 20 Years Before Death. *JAMA Intern Med.* 2017.

221. Mulrow CD, Cornell JA, Herrera CR, Kadri A, Farnett L, Aguilar C. Hypertension in the elderly. Implications and generalizability of randomized trials. *Jama.* 1994;272(24):1932-1938.

222. Fried TR, Tinetti ME, Iannone L, O'Leary JR, Towle V, Van Ness PH. Health outcome prioritization as a tool for decision making among older persons with multiple chronic conditions. *Arch Intern Med.* 2011;171(20):1854-1856.

223. Walma EP, Hoes AW, van Dooren C, Prins A, van der Does E. Withdrawal of long-term diuretic medication in elderly patients: a double blind randomised trial. *Bmj.* 1997;315(7106):464-468.

224. Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. *Jama.* 1998;279(11):839-846.

225. Bradley MC, Fahey T, Cahir C, et al. Potentially inappropriate prescribing and cost outcomes for older people: a cross-sectional study using the Northern Ireland Enhanced Prescribing Database. *European journal of clinical pharmacology.* 2012;68(10):1425-1433.

226. Nederlandse Internisten Vereniging, Nederlandse Vereniging voor Klinische Geriatrie. Addendum (kwetsbare) ouderen bij CVRM. 2017: https://richtlijnendatabase.nl/richtlijn/addendum_kwetsbare_ouderen_bij_cvrm. Accessed 01-02-2018.

227. Luymes CH, van der Kleij RM, Poortvliet RK, de Ruijter W, Reis R, Numans ME. Deprescribing Potentially Inappropriate Preventive Cardiovascular Medication: Barriers and Enablers for Patients and General Practitioners. *Ann Pharmacother.* 2016;50(6):446-454.

228. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. *Bmj.* 2015;351:h4672.

229. Moll van Charante EP, Richard E, Eurelings LS, et al. Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *Lancet.* 2016;388(10046):797-805.

230. Zanchetti A, Liu L, Mancia G, et al. Blood pressure and LDL-cholesterol targets for prevention of recurrent strokes and cognitive decline in the hypertensive patient: design of the European Society of Hypertension-Chinese Hypertension League Stroke in Hypertension Optimal Treatment randomized trial. *Journal of hypertension.* 2014;32(9):1888-1897.

231. Wang P, Wang Y, Feng T, et al. Rationale and design of a double-blind, placebo-controlled, randomized trial to evaluate the safety and efficacy of nimodipine in preventing cognitive impairment in ischemic cerebrovascular events (NICE). *BMC Neurol.* 2012;12:88.

232. Hoevenaar-Blom MP, Guillemont J, Ngandu T, et al. Improving data sharing in research with context-free encoded missing data. *PLoS One.* 2017;12(9):e0182362.

233. Donohue MC, Sperling RA, Salmon DP, et al. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol*. 2014;71(8):961-970.

234. Turnbull F, Neal B, Ninomiya T, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. *Bmj*. 2008;336(7653):1121-1123.

235. Iijn Nze. Zorg door de huisarts: Jaarcijfers 2016 en trendijfers 2011-2016. 2017. https://www.nivel.nl/sites/default/files/jaarrapport_huisarts_2016.pdf. Accessed 02-02-2018.

236. Spaar A, Frey M, Turk A, Karrer W, Puhan MA. Recruitment barriers in a randomized controlled trial from the physicians' perspective: a postal survey. *BMC Med Res Methodol*. 2009;9:14.

237. Lawlor B, Kennelly S, O'Dwyer S, et al. NILVAD protocol: a European multicentre double-blind placebo-controlled trial of nilvadipine in mild-to-moderate Alzheimer's disease. *BMJ Open*. 2014;4(10):e006364.

238. Meulenbroek O, O'Dwyer S, de Jong D, et al. European multicentre double-blind placebo-controlled trial of Nilvadipine in mild-to-moderate Alzheimer's disease-the substudy protocols: NILVAD frailty; NILVAD blood and genetic biomarkers; NILVAD cerebrospinal fluid biomarkers; NILVAD cerebral blood flow. *BMJ Open*. 2016;6(7):e011584.

LIST OF ABBREVIATIONS

ACCORD-MIND	*Action to Control Cardiovascular Risk in Diabetes Memory in Diabetes*
ACE	Angiotensin converting enzyme
ADVANCE	*Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation*
AHM	Antihypertensive medication
AMC	Academic Medical Center
ARB	Angiotensin receptor blocker
ARV	Average real variability
BMI	Body mass index
BP	Blood pressure
CCB	Calcium channel blockers
CI	Confidence interval
CINAHL	*Cumulative Index to Nursing and Allied Health Literature*
COREQ	Consolidated criteria for reporting qualitative research
CV	Coefficient of variation
CVD	Cardiovascular disease
DANTE	*Discontinuation of Antihypertensive Treatment in Elderly People*
DBP	Diastolic blood pressure
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders IV
EVA	*Evaluation of Vascular Care in Alzheimer's Disease*
FINGER	*Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability*
GP	General practitioner
GRADE	*Grading of Recommendations, Assessment, Development and Evaluations*
HATICE	*Healthy Ageing Through Internet Counselling in the Elderly*
HR	Hazard ratio
i.e.	Id est ('that is')
IPD	Individual participant data
IQR	Interquartile range
LDL	Low-density lipoprotein
LIBRA	*LIfestyle for BRAin health*
Look AHEAD	*Look Action for Health in Diabetes*
MAPT	*Multidomain Alzheimer Preventive Trial*
MD	Mean difference
MMSE	Mini-mental state examination

MRI	Magnetic Resonance Imaging
NICE	*Nimodipine Preventing Cognitive Impairment in Ischemic Cerebrovascular Event*
PreDIVA	*Prevention of Dementia by Intensive Vascular Care*
PRISMA	*Preferred Reporting Items for Systematic Reviews and Meta-analyses*
PRoFESS	*Prevention Regimen for Effectively Avoiding Second Strokes*
PROGRESS	*Perindopril Protection Against Recurrent Stroke Study*
RCT	Randomised controlled trial
RR	Risk ratio
SBP	Systolic blood pressure
SCOPE	*Study on Cognition and Prognosis in the Elderly*
SD	Standard deviation
SMD	Standardized mean difference
SPRINT	*Systolic Blood Pressure Intervention Trial*
SPRINT-MIND	*Systolic Blood Pressure Intervention Trial memory and cognition in decreased hypertension*
START	*Screening Tool to Alert doctors to Right Treatment*
STOPP	*Screening Tool of Older Person's Prescriptions*
SVD	Small vessel disease
Syst-Eur	*Systolic Hypertension in Europe*
TBV	Total brain volume
TIA	Transient ischemic attack
VAT	Visual Association Test
VIM	Variation independent of mean
VVV	Visit-to-visit variability
WMH	White matter hyperintensities

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DATA MANAGEMENT STATEMENT

PreDIVA trial

The raw data from the preDIVA trial was originally completed on paper and afterwards entered, in duplicate, in an electronic system. This electronic dataset is anonymized with unique identifiers and is stored at the Academic Medical Center Server, only available for members of the research group. The data is not yet made openly available, as currently several secondary analyses are still ongoing.

Qualitative data

The interviews with general practitioners and HATICE intervention participants were audio taped. These audiotapes, together with their written transcripts, coded files and analysis files are anonymized and stored at the Academic Medical Center server, only available for members of the research group.

LIST OF PUBLICATIONS

1. **van Middelaar T**, Nederkoorn PJ, van der Worp HB, Stam J, Richard E. Quality of life after surgical decompression for space-occupying middle cerebral artery infarction: systematic review. *Int J Stroke*. 2015;10:170-6.
2. **van Middelaar T**, Richard E, van der Worp HB, van den Munckhof P, Nieuwkerk PT, Visser MC, Stam J, Nederkoorn PJ. Quality of life after surgical decompression for a space-occupying middle cerebral artery infarct: A cohort study. *BMC Neurol*. 2015;15:156.
3. **van Middelaar T**, Richard E, Visser MC, van den Munckhof P, Stam J, Nederkoorn PJ. Kwaliteit van leven na hemicraniëctomie wegens een ruimte-innemend herseninfarct. *Tijdschr Neurol Neurochir*. 2016;117:63-6.
4. Jongstra S, Beishuizen C, Andrieu S, Barbera M, van Dorp M, van de Groep B, Guillemont J, Mangialasche F, **van Middelaar T**, Moll van Charante E, Soininen H, Kivipelto M, Richard E. Development and Validation of an Interactive Internet Platform for Older People: The Healthy Ageing Through Internet Counselling in the Elderly Study. *Telemed J E Health*. 2017;23(2):96-104.
5. **van Middelaar T**, van Vught LA, Moll van Charante EP, Eurelings LSM, Ligthart SA, van Dalen JW, van den Born BJH, Richard E, van Gool WA. Lower dementia risk with different classes of antihypertensive medication in older patients. *J Hypertens*. 2017 Oct;35(10):2095-2101.
6. Goedemans T, Verbaan D, Coert BA, Kerklaan BJ, van den Berg R, Coutinho JM, **van Middelaar T**, Nederkoorn PJ, Vandertop WP, van den Munckhof P. Neurologic Outcome After Decompressive Craniectomy: Predictors of Outcome in Different Pathologic Conditions. *World Neurosurg*. 2017;105:765-774.
7. **van Middelaar T**, Beishuizen CRL, Guillemont J, Barbera M, Richard E, Moll van Charante EP. Engaging older people in an internet platform for cardiovascular risk self-management: a qualitative study among Dutch HATICE participants. *BMJ Open*. 2018;8(1):e019683.
8. **van Middelaar T**, van Dalen JW, van Gool WA, van den Born BH, van Vught LA, Moll van Charante EP, Richard E. Visit-to-visit blood pressure variability and the risk of dementia in older people. *J Alzheimers Dis*. 2018;62(2):727-735.
9. **van Middelaar T**, Ivens SD, van Peet PG, Poortvliet RKE, Richard E, Pols AJ, Moll van Charante EP. Prescribing and deprescribing antihypertensive medication in older people by Dutch general practitioners: a qualitative study. *BMJ Open*. 2018;8(4):e020871.

10. **van Middelaar T**, Argillander TE, Schreuder FHBM, Deinum J, Richard E, Klijn CJM. Effect of antihypertensive medication on cerebral small vessel disease: a systematic review and meta-analysis. *Stroke*. 2018;49(6):1531-1533.
11. **van Middelaar T**, van Vught LA, van Gool WA, Simons EMF, van den Born BH, Moll van Charante EP, Richard E. Blood-pressure-lowering interventions to prevent dementia: a systematic review and meta-analysis. *J Hypertens*. 2018. doi: 10.1097/HJH.0000000000001829.
12. **van Middelaar T**, Hoevenaar-Blom MP, van Gool WA, Moll van Charante EP, van Dalen JW, Deckers K, Köhler S, Richard E. *Alzheimers Res Ther*. 2018;10(1):62.

Submitted

1. **van Middelaar T**, Moll van Charante EP. Deprescribing preventive medication in older patients - urgent need for more awareness. *Accepted for publication in BJGP*.
2. Coley N*, Rosenberg A*, **van Middelaar T***, Soulier A, Barbera M, Guillemont J, Steensma J, Igier V, Eskelinen M, Soininen H, Moll van Charante EP, Richard E, Kivipelto M, Andrieu S, for the MIND-AD and HATICE groups. Older Europeans' reasons for participating in a multinational eHealth prevention trial: a cross-country comparison using mixed methods (ACCEPT-HATICE).
3. Peters R, Yasar S, Anderson CS, Andrews S, Antikainen R, Arima H, Beckett N, Beer JC, Bertens AS, Booth A, van Boxtel M, Brayne C, Brodaty H, Carlson MC, Chalmers J, Corrada MM, DeKosky S, Derby C, Dixon RA, Forette F, Ganguli M, van Gool WA, Guaita A, Hever A, Hogan DB, Jagger C, Katz M, Kawas C, Kehoe PG, Keinanen-Kiukaanniemi S, Kenny R, Köhler S, Kunutsor S, Laukkanen J, Maxwell C, McFall GP, **van Middelaar T**, Moll van Charante EP, MRC CFAS, Ng TP, Peters J, Rawtaer I, Richard E, Rockwood K, Rydén L, Sachdev P, Skoog I, Skoog J, Staessen JA, Stephan BCM, Sebert S, Thijs L, Trompet S, Tully PJ, Tzourio C, Vaccaro R, Varamo E, Walsh E, Wang C, Warwick J, Anstey KJ. Class doesn't matter. An investigation of antihypertensive class effects on dementia and cognitive decline: A meta-analysis of participant data.
4. Richard E, Moll van Charante EP, Hoevenaar-Blom EP, Coley N, Barbera M, van der Groep A, Meiller Y, Mangialasche F, Beishuizen CB, Jongstra S, **van Middelaar T**, van Wanrooij LL, Ngandu T, Guillemont J, Andrieu SA, Brayne C, Kivipelto M, Soininen H, van Gool WA. Healthy Ageing Through Internet Counselling in the Elderly (HATICE) - a multinational randomized controlled trial.
5. **van Middelaar T**, Richard E, Moll van Charante EP, van Gool WA, van Dalen J. Visit-to-visit blood pressure variability and progression of white matter hyperintensities.

PHD PORTFOLIO

Courses

2015

- Refresher course in statistics, Nijmegen (1.5 ECTS)
- Research data management for PhD's, Nijmegen (0.2 ECTS)
- Basic Legislation in Science (BROK), Nijmegen (1.0 ECTS)
- Qualitative research methods, Amsterdam (1.9 ECTS)

2016

- Academic writing, Nijmegen (3.0 ECTS)

2017

- Advanced topics in biostatistics, Amsterdam (2.1 ECTS)
- Neuroanatomy, hands-on dissection course, Nijmegen (1.0 ECTS)
- Multilevel and events history analysis using R, Nijmegen (2.0 ECTS)

2018

- Scientific Integrity course, Nijmegen (0.3 ECTS)

Seminars & workshops

2016

- Utrechtse Stroke Update, Utrecht.

2017

- Mobile Health symposium, Amsterdam Center for Health Communication, Amsterdam.

Oral presentations

2016

- Nederlandse Vereniging voor Neurologie-wetenschapsdagen, Nunspeet: *"Antihypertensiva en dementie"*

2017

- European Stroke Organisation Conference, Prague: "*Lower dementia risk with different classes of antihypertensiva medication in older patients"*
- Nederlandse Vereniging voor Neurologie-wetenschapsdagen, Nunspeet: *"Het effect van antihypertensiva op de progressie van cerebrale small vessel disease: een systematische review en meta-analyse"*

(Inter)national conferences

2015

- Nederlands Huisartsen Genootschap (NHG) Wetenschapsdag, Rotterdam.
- World Organization of Family Doctors (WONCA) conference, Istanbul.

2016

- European Stroke Organisation Conference, Barcelona.
- Nederlands Huisartsen Genootschap (NHG) Wetenschapsdag, Amsterdam.
- International meeting of The International Society of Vascular Behavioural and Cognitive Disorders (VasCog), Amsterdam.
- Nederlandse Vereniging voor Neurologie-wetenschapsdagen, Nunspeet.

2017

- European Stroke Organisation Conference, Prague.
- Alzheimer's Association International Conference (AAIC), London.
- Nederlands Huisartsen Genootschap (NHG) Wetenschapsdag, Zeist.
- Nederlandse Vereniging voor Neurologie-wetenschapsdagen, Nunspeet.

Parameters of esteem

2017

- Neurology reviews, conference coverage: *Can Antihypertensive Medication Reduce Dementia Risk in Older Adults?* 2017 December; 25(12):40-41.

2017

- Nomination for the Student Poster Competition, Alzheimer's Association International Conference.

2016

- Nomination for the Young Investigator Poster Award, VasCog.

Grants

2017

- Grant for an international conference, Alzheimer Nederland.

Other

2015

- General assembly meeting MIND-AD, Stockholm
- General assembly meeting HATICE and MIND-AD, Amsterdam
- General assembly meeting HATICE and MIND-AD, Cambridge

2016

- General assembly meeting HATICE and MIND-AD, Amsterdam

2017

- General assembly meeting HATICE and MIND-AD, Paris
- General assembly meeting HATICE and MIND-AD, Stockholm

Lecturing

2016 & 2017

- E-Health lecture for Medical Information Sciences students
- Neurological examination training and exam for Medical students

Tutoring & mentoring

- Sophie Ivens, three month internship during general practitioner speciality training, qualitative research "*antihypertensiva beleid van huisartsen*"
- Nicole Waalders, bachelor student Medicine, "*responder analyses in preDIVA*"
- Jaap Steensma, master student Medicine, qualitative research "*reasons for participation in HATICE*" and quantative research "determinants of adherence in HATICE".

CURRICULUM VITAE

Tessa van Middelaar was born in 1989 in Woerden. After graduating from the Kalsbeek College she studied Psychology at the University of Amsterdam for one year. Her wish to study Medicine was fulfilled in 2008. During her education she performed a scientific study on the quality of life after a hemicraniectomy for a malignant infarct. Tessa was able to incorporate this scientific experience and a training in didactic skills in the honours master programme. In 2015 she graduated and was directly able to start her PhD training at the Radboud University Medical Center and Academic Medical Center. Currently she works as neurology resident at 'Noordwest Ziekenhuisgroep' at Alkmaar. Tessa lives together with her partner Jordy M. Klijn.

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Edo Richard, toen je mij vroeg naar Nijmegen mee te gaan voor een promotietraject was mijn keuze snel gemaakt. Daarbij was het vooral van belang dat ik je tijdens mijn stage al had leren kennen als een ontzettend fijne begeleider. Je tomeloze enthousiasme, brede interesse, gedrevenheid, maar ook het feit dat je altijd voor iedereen klaar staat, waren daarin doorslaggevend. En daar heb je me niet in teleurgesteld. Ook je steun in mijn vervolg traject richting de neurologie is geweldig. Eric Moll van Charante, je maakt het team compleet door je filosofische blik. Daar waar ik soms te snel en oppervlakkig door het kwalitatieve werk heen ging, spoorde je me aan nog een laag dieper te kijken en er nog wat langer over na te denken. Het is ook inspirerend om te zien hoe je een goede balans weet te vinden tussen je werk en privé leven.

Veel dank aan alle commissieleden (Prof. dr. W.J.J.. Assendelft, Prof. dr. M. Muller, Prof. dr. F.R.J. Verhey, dr. E. van Dijk en Prof. dr. N.P. Riksen) voor hun bereidheid om zitting te nemen in de promotiecommissie en mijn proefschrift te beoordelen.

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DISSERTATIONS OF THE DISORDERS OF MOVEMENT RESEARCH GROUP, NIJMEGEN

Vascular disorders of movement – The Radboud Stroke centre

- Liselore Snaphaan. Epidemiology of post stroke behavioral consequences. Radboud University Nijmegen, 12 March 2010
- Karlijn F. de Laat. Motor performance in individuals with cerebral small vessel disease: an MRI study. Radboud University Nijmegen, 29 November 2011
- Anouk G.W. van Norden. Cognitive function in elderly individuals with cerebral small vessel disease. An MRI study. Radboud University Nijmegen, 30 November 2011
- Rob Gons. Vascular risk factors in cerebral small vessel disease. A diffusion tensor imaging study. Radboud University Nijmegen, 10 December 2012
- Loes C.A. Rutten-Jacobs. Long-term prognosis after stroke in young adults. Radboud University Nijmegen, 14 April 2014
- Noortje A.M.M. Maaijwee. Long-term neuropsychological and social consequences after stroke in young adults. Radboud University Nijmegen, 12 June 2015
- Nathalie E. Synhaeve. Determinants of long-term functional prognosis after stroke in young adults. Radboud University Nijmegen, 28 September 2016
- Anil M. Tuladhar. The disconnected brain: mechanisms of clinical symptoms in small vessel disease. Radboud University Nijmegen, 4 October 2016
- Pauline Schaapsmeerders. Long-term cognitive impairment after first-ever ischemic stroke in young adults: a neuroimaging study. Radboud Univesity Nijmegen, 24 January 2017
- Ingeborg W.M. van Uden. Behavioural consequences of cerebral small vessel disease; an MRI approach. Radboud University Nijmegen, 14 February 2017
- Renate M. Arntz. The long-term risk of vascular disease and epilepsy after stroke in young adults. Radboud University Nijmegen, 16 February 2017
- Helena M. van der Holst. Mind the step in cerebral small vessel disease. Brain changes in motor performance. Radboud University Nijmegen, 5 April 2017
- Joyce Wilbers. Long-term neurovascular complications in cancer patients. Radboud University Nijmegen, 25 September 2017.
- Frank G. van Rooij. Transient neurological attacks. Neuroimaging, etiology, and cognitive consequences. Radboud University Nijmegen, 14 June 2018.

Parkinson Center Nijmegen (ParC)

- Jasper E. Visser. The basal ganglia and postural control. Radboud University Nijmegen, 17 June 2008
- Maaike Bakker. Supraspinal control of walking: lessons from motor imagery. Radboud University Nijmegen, 27 May 2009
- W. Farid Abdo. Parkinsonism: possible solutions to a diagnostic challenge. Radboud University Nijmegen, 7 October 2009
- Samyra H.J. Keus. Physiotherapy in Parkinson's disease. Towards evidence-based practice. Leiden University, 29 April 2010
- Lars B. Oude Nijhuis. Modulation of human balance reactions. Radboud University Nijmegen, 29 November 2010

- Maarten J. Nijkrake. Improving the quality of allied health care in Parkinson's disease through community-based networks: the ParkinsonNet health care concept. Radboud University Nijmegen, 29 November 2010
- Rick C.G. Helmich. Cerebral reorganization in Parkinson's disease. Radboud University Nijmegen, 24 May 2011
- Charlotte A. Haaxma. New perspectives on preclinical and early stage Parkinson's disease. Radboud University Nijmegen, 6 December 2011
- Johanna G. Kalf. Drooling and dysphagia in Parkinson's disease. Radboud University Nijmegen, 22 December 2011
- Anke H. Snijders. Tackling freezing of gait in Parkinson's disease. Radboud University Nijmegen,4 June 2012
- Bart F.L. van Nuenen. Cerebral reorganization in premotor parkinsonism. Radboud University Nijmegen, 22 November 2012
- Wandana Nanhoe-Mahabier. Freezing of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, 13 February 2013
- Marlies van Nimwegen. Promotion of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, 6 March 2013
- Arlène D. Speelman. Promotion of physical activity in Parkinson's disease, feasibility and effectiveness. Radboud University Nijmegen, 6 March 2013
- Tjitske Boonstra. The contribution of each leg to bipedal balance control. University Twente, 6 June 2013
- Marjolein A van der Marck. The Many faces of Parkinson's disease: towards a multifaceted approach? Radboud University Nijmegen, 10 January 2014
- Katrijn Smulders. Cognitive control of gait and balance in patients with chronic stroke and Parkinson's disease. Radboud University Nijmegen, 21 May 2014
- Marjolein B. Aerts. Improving diagnostic accuracy in parkinsonism. Radboud University Nijmegen, 27 June 2014
- Maartje Louter. Sleep in Parkinson's disease. A focus on nocturnal movements. Radboud University Nijmegen, 13 February 2015
- Frederick Anton Meijer. Clinical Application of Brain MRI in Parkinsonism: From Basic to Advanced Imaging, Radboud University Nijmegen, 23 June 2015
- Jorik Nonnekes. Balance and gait in neurodegenerative disease: what startle tells us about motor control, Radboud University Nijmegen, 2 September 2015
- Martijn van der Eijk. Patient-centered care in Parkinson's disease. Radboud University Nijmegen, 1 December 2015
- Ingrid Sturkenboom. Occupational therapy for people with Parkinson's disease: towards evidence-informed care. Radboud University Nijmegen, 11 February 2016
- Merel M. van Gilst. Sleep benefit in Parkinson's disease. Radboud University Nijmegen, 13 April 2016
- Arno M. Janssen. Transcranial magnetic stimulation - measuring and modeling in health and disease. Radboud University Nijmegen, 2 June 2016
- Annette Plouvier. De ziekte van Parkinson, een gezamenlijke reis van huisarts en patient. Radboud University Nijmegen, 15 June 2017

- Nico Weerkamp. Parkinson's disease in long-term-care facilities. Radboud University Nijmegen, 1 September 2017
- Freek Nieuwhof. The complexity of walking: cognitive control of gait in aging and Parkinson's disease. Radboud University Nijmegen, 27 October 2017

Non-Parkinsonian disorders of movement

- Sacha Vermeer. Clinical and genetic characterization of autosomal recessive cerebellarataxias. Radboud University Nijmegen, 5 April 2012
- Susanne T. de Bot. Hereditary spastic paraplegias in the Netherlands. Radboud University Nijmegen, 20 December 2013
- Catherine C.S. Delnooz. Unraveling primary focal dystonia. A treatment update and new pathophysiological insights. Radboud University Nijmegen, 7 January 2014
- Ella MR Fonteyn. Falls, physiotherapy, and training in patients with degenerative ataxias, 29 June 2016
- Britt S. Hoffland. Investigating the role of the cerebellum in idiopathic focal dystonia. Radboud University Nijmegen, 22 March 2018

Neuromuscular disorders of movement

- Mireille van Beekvelt. Quantitative near infrared spectroscopy (NIRS) in human skeletal muscle. Radboud University Nijmegen, 24 April 2002
- Johan Hiel. Ataxia telangiectasia and Nijmegen Breakage syndrome, neurological, immunological and genetic aspects. Radboud University Nijmegen, 23 April 2004
- Gerald JD Hengstman. Myositis specific autoantibodies, specificity and clinical applications. Radboud University Nijmegen, 21 September 2005
- M. Schillings. Fatigue in neuromuscular disorders and chronic fatigue syndrome, a neurophysiological approach. Radboud University Nijmegen, 23 November 2005
- Bert de Swart. Speech therapy in patients with neuromuscular disorders and Parkinson's disease. Diagnosis and treatment of dysarthria and dysphagia. Radboud University Nijmegen, 24 march 2006
- J. Kalkman. From prevalence to predictors of fatigue in neuromuscular disorders. The building of a model. Radboud University Nijmegen, 31 October 2006
- Nens van Alfen. Neuralgicamyotrophy. Radboud University Nijmegen, 1 November 2006
- Gea Drost. High-density surface EMG, pathophysiological insights and clinical applications. Radboud University Nijmegen, 9 March 2007
- Maria Helena van der Linden. Pertubations of gait and balance: a new experimental setup applied to patients with CMT type 1a. Radboud University Nijmegen, 6 October 2009
- Jeroen Trip. Redefining the non-dystrophic myotonic syndromes. Radboud University Nijmegen, 22 January 2010
- Corinne G.C. Horlings. A weak balance: balance and falls in patients with neuromuscular disorders. Radboud University Nijmegen, 1 April 2010
- E. Cup. Occupational therapy, physical therapy and speech therapy for persons with neuromuscular diseases, an evidence based orientation. Radboud University Nijmegen, 5 July 2011

- Alide Tieleman. Myotonic dystrophy type 2, a newly diagnosed disease in the Netherlands. Radboud University Nijmegen, 15 July 2011
- Nicol Voermans. Neuromuscular features of Ehlers-Danlos syndrome and Marfan syndrome. Radboud University Nijmegen, 2 September 2011
- Allan Pieterse. Referral and indication for occupational therapy, physical therapy and speech-language therapy for persons with neuromuscular disorders. Radboud University Nijmegen, 13 February 2012
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- M. Minis. Sustainability of work for persons with neuromuscular diseases. Radboud University Nijmegen, 13 November 2013
- Willemijn Leen. Glucose transporter – 1 deficiency syndrome. Radboud University Nijmegen, 26 June 2014
- Barbara Jansen. Magnetic Resonance Imaging signature of fascioscpulohumeral muscular dystrophy. Radboud University Nijmegen. 14 September 2015
- Noortje Rijken. Balance and gait in FSHD, relations with individual muscle involvement. Radboud University Nijmegen, 8 December 2015
- Femke Seesing. Shared Medical appointments for neuromuscular patients and their partners. Radboud University Nijmegen, 2 September 2016
- Nicole Voet. Aerobic exercise and cognitive behavioral therapy in fascioscapulohumeral dystrophy: a model based approach. Radboud University Nijmegen, 14 October 2016.
- Barbara van der Sluijs. Oculopharyngeal muscular dystrophy (OPMD) in the Netherlands. Beyond dysphagia and ptosis. Radboud University Nijmegen, 11 December 2017

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